Research Square

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Age-stratified association between plasma adiponectin levels and morality in septic patients

Hui Wang
China-Japan Friendship Hospital
Ming Ma
Yan-xiang Gao
China-Japan Friendship Hospital
Yi-na Wu
China-Japan Friendship Hospital
Shan-shan Zhai
China-Japan Friendship Hospital
Chen Li
China-Japan Friendship Hospital
Jun Duan (Duanjun_cjfh@126.com)
China-Japan Friendship Hospital

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Abstract

Background: Plasma adiponectin (APN) levels are might be affected by age. The present study aimed to study the association between plasm APN levels and age, and the effects of APN levels on mortality in different age-stratified septic patients.

Methods: The retrospective study that was performed with 173 patients with sepsis and 57 controls. Physical and demographic characteristics were recorded, blood samples were collected to measure plasma adiponectin levels. Using these data, we determined the association between plasma adiponectin levels and age, and the effect of plasma adiponectin levels on mortality in different age-stratified septic patients.

Results: Three age group were defined: middle-age patients range of <60years, the old group of 60-80 years, and the elderly group of ≥80years. Plasma adiponectin levels increased with increasing age both in control group and sepsis group. Mortality increased with age: 12.3% in middle-aged patients, 24.6% in old patients, and 36.2% in elderly patients (P<0.001). In middle-age patients and old patients, according to the receiver operating characteristic curve, plasma APN levels had the comparable value in prediction of 28-day mortality. And adiponectin levels were an independent predictive factor for 28-day mortality for patients <80 years. However, in elderly patients, the adiponectin levels showed no significant association with 28-day mortality.

Conclusions: A significant positive association between plasma APN levels and age in septic patients were found. Low circulating levels of APN were associated with 28-day mortality in septic patients aged <80years. The association between APN and mortality in sepsis patients aged >80years were not significantly found.

Introduction

In recent years, the growing proportion of older adults in general patient population, contributing to a rise in intensive care unit admissions, and increased mortality among critically ill older adults[1–3]. Due to demographic changes, older adults constitute a growing proportion among critically ill patients. The clinical status of these patients is often burdened by multiple underlying comorbidities, making them particularly vulnerable to more complications when in condition of infection. Many critical care studies have focused on older adults.

Adiponectin (APN), a collagen-like peptide secreted exclusively by adipose tissue, and has several biological activities, including enhancing insulin sensitivity and modulating lipid metabolism[4, 5]. Decreased adiponectin bioactivity has been implicated in condition of the “metabolic syndrome” such as obesity, type 2 diabetes, and cardiovascular diseases[6, 7].In addition to its well-known metabolic function, APN exerts anti-inflammatory effects[8, 9]. Recent studies in people have shown that APN is negatively correlated with other pro-inflammatory cytokines and illness severity scores and is also a

strong negative prognostic indicator for mortality in septic patients[10, 11]. We previously also found that low APN-level were associated with 28-day mortality in sepsis patients[12].

There are also several reports that age is associated with elevated plasma APN levels in healthy adults, despite the higher cardiovascular risk in elderly individuals[13–16]. The underlying mechanisms of age-related increase in plasma APN levels are examined in several reports that might be associated with visceral fat[15] and renal function[14, 16]. Furthermore, it has been reported the relationship between age and plasma APN levels in some pathological conditions, such as type 2 diabetes[17]. However, in the other pathological conditions, whether age is also associated with plasma APN levels is unknown, and the age-related changes should be taken into account.

Therefore, the present study aimed to investigate the association between plasma APN levels and age, and the mortality of sepsis in different age stratification in the pathological condition of sepsis.

Results

Clinical characteristics of patients

The present study included 173 patients with sepsis with a mean age of 67.58 ± 14.07 years. All participants in both the sepsis and control group were stratified into 3 age groups based on the age ranges of < 60years (the middle-aged group), 60-80years (the old group) and > 80years (the elderly group). The main sources of sepsis were gastrointestinal in 67 patients (38.7%), pulmonary in 55 patients (31.8%), cholangitis in 28 patients (16.2%), genitourinary in 14 patients (8.1%), and bloodstream infection in 9 patients (5.2%). Patients' characteristics are shown in Table 1. Hypertension, diabetes mellitus, coronary artery disease and chronic kidney disease were reported more frequently in elderly patients compare with the other groups. Patients in the elderly patients had significantly higher APACHE II scores, serum creatinine, BNP, and CRP than the other groups. No differences were observed between the age groups in terms of male gender, SOFA scores and the other laboratory parameters in Table 1.

Table 1
Clinical characteristics of patients with sepsis at admission.

	Middle-aged patients (< 60 years)(n = 57)	Old patients (60–79) (n = 69)	Elderly patients (≥ 80 years) (n = 47)	p
Age (years)	54 (45–56)	70 (66-75.5)	84 (81–85)	< 0.0001
Male (n [%])	25 (43.9)	39 (56.5)	26 (55.3)	0.319
BMI (kg/m^2)	23.04 (20.96–24.54)	23.43 (21.6-25.18)	22.89 (19.63–25.28)	0.588
Past illness				
Hypertension (n [%])	19 (33.3)	37 (53.6)	32 (68.1)	0.002
Diabetes (n [%])	10 (17.5)	41 (59.4)	36 (76.6)	< 0.0001
CAD (n [%])	17(29.8)	31(44.9)	26(55.3)	0.02
CKD (n [%])	11(19.3)	29(42.0)	24(51.1)	0.003
Severity of illness				
APACHE II score	16 (11–24)	19 (14–23)	23 (19–28)	0.0001
SOFA score	11 (7.5–15)	9 (6-13.5)	10 (7–12)	0.362
Laboratory parameters				
Glucose (mmol/L)	11.3 (9.4–14.3)	11.7 (9.4–15.4)	10.7 (9.5–12.5)	0.249
Scr (μmol/L)	106.2 (75.7-173.3)	132.2 (75.3-239.5)	174.4 (108-263.5)	0.003
ALT (IU/L)	37 (19.5–76.5)	31 (14–71)	21 (12–81)	0.488
BNP (pg/ml)	840.5 (302–1442)	1133 (545–2066)	1328 (661.9–5053)	0.005
hsTnT (ng/ml)	0.122 (0.024–0.482)	0.056 (0.012–0.486)	0.192 (0.04–0.643)	0.067
PCT (ng/ml)	6.86 (3.12–20.75)	11.96 (3.73–24.85)	8.71 (1.08–33.4)	0.185
CRP (mg/L)	24.24 (13.51–55.2)	45 (15.8-96.13)	76.18 (45.26–145)	< 0.0001
Lactic acid (mmol/L)	3.2 (1.9–4.75)	2.6 (1.6–3.9)	2.3 (1.9–4.4)	0.219

	Middle-aged patients (< 60 years)(n = 57)	Old patients (60–79) (n = 69)	Elderly patients (≥ 80 years) (n = 47)	p
APN(μg/ml)	6.34 (3.35–8.49)	8.32 (4.77–10.34)	9.87 (7.58–12.33)	0.0001
Clinical outcomes				
Invasive ventilation duration (d)	4 (1–9)	5 (2–19)	15 (7–27)	0.0003
28-day mortality (n [%])	7 (12.3)	17 (24.6)	17 (36.2)	0.013
In-hospital mortality (n [%])	9 (15.8)	19 (27.5)	18 (38.2)	0.034

The data are expressed as median with IQRs or number (%) of patients. Comparison between groups were performed using Kruskal-Wallis test for continuous variables and $\chi 2$ tests for categorical data. BMI, Body Mass Index; CAD, coronary artery disease; CKD, chronic kidney disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; Scr, serum creatinine; ALT, alanine transaminase; BNP, brain natriuretic; hsTnT, high-sensitivity troponin T; PCT, procalcitonin; CRP, C reactive protein; APN, adiponectin.

Variation in APN levels in sepsis patients

Plasma APN levels in each age group are shown in Table 1 and Fig. 1. Plasma APN levels were significantly lower in patients with sepsis than those in patients without sepsis in all age groups, and increased with age in both groups. The plasma APN level was negatively correlated with age in both control group and sepsis group ($r = 0.690$, $p < 0.0001$ and $r = 0.412$, $p < 0.0001$; Fig. 2).

Comparison of clinical outcomes

The results of the comparison of clinical outcomes in all age stratified groups are shown in Table 1. In the unadjusted analysis, the elderly patients had significantly 28-day mortality and in-hospital mortality (36.2% vs. 24.6% vs. 12.3%, $p = 0.013$; 38.2% vs. 27.5% vs. 15.8%, $p = 0.034$), longer duration of mechanical ventilator (15 (IQR: 7–27) vs. 5 (IQR: 2–19) vs. 4 (IQR: 1–9)) than the old patients and middle-age patients. Results of subgroup analysis of 28-day mortality in patients with sepsis are summarized in Fig. 3 and Table 2. Figure 3A shows the survival curve for the distinct age groups. Compared with the middle-aged patients, cumulative survival was significantly lower in the other two older age categories. In the subgroup of deceased patients, the elderly patients had higher plasma APN levels than the other two groups, and the plasma APN level was negatively correlated with age in the deceased patients ($r = 0.386$, $p = 0.007$; Table 2, Fig. 3B).

Table 2
Comparison of serum APN levels in sepsis patients of different ages according to the type of patient survival.

Patients with sepsis	APN (ng/ml)			p
	< 60 years	60–80 years	> 80 years	
Surviving patients	6.53 (4.4–8.54)	8.91 (6.19–10.45)	9.9 (8.28–14.6)	< 0.0001
Deceased patients	4.98 (3.1–7.65)	5.34 (2.73–9.33)	9.08 (6.45–11.53)	0.009

APN, Adipnectin.

Association between APN and mortality in different age stratification

As we found that both the in-hospital mortality and APN levels increased with age, different from our previous studies that low APN levels are associated with mortality in sepsis [12]. We further investigated the association between APN level and 28-day mortality in different age stratification.

We first performed univariate logistic regression analyses of all parameters in different age stratification (Table 3), and found that low APN levels were associated with a high risk of death within 28 days for both sepsis patients < 60 years and 60–80 years of age (OR = 0.389, 95%CI = 0.181–0.632, p < 0.0001 and OR = 0.687, 95%CI = 0.540–0.840, p < 0.000, respectively). Other parameters, including APACHE II scores and SOFA scores both in < 60 years and 60-80years group, and serum creatinine, BNP and CRP only in 60–80 years group, also significantly influenced 28-day mortality. However, in > 80 years patients with sepsis, excepting for the APACHE II scores and BNP level, the other parameters showed no significant relationship with 28-day mortality, including the plasma APN levels.

Table 3
Univariate logistic regression analysis of factors associated with 28-day mortality in different age stratification.

Varible	< 60 years			60-80years			> 80 years		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Sex	0.825	0.189–3.274	0.787	0.805	0.276–2.356	0.688	1.467	0.448–5.003	0.528
BMI	1.032	0.791–1.368	0.819	1.024	0.839–1.254	0.815	0.979	0.813–1.176	0.825
Hypertension	0.830	0.162–3.442	0.289	1.269	0.439–3.787	0.660	1.368	0.388–5.258	0.630
Diabetes	0.756	0.148–3.122	0.711	2.800	0.918–9.743	0.082	0.678	0.171–2.763	0.579
CAD	2.917	0.702–12.29	0.134	2.063	0.712–6.207	0.182	1.467	0.448–5.003	0.528
CKD	2.089	0.388–9.389	0.366	2.593	0.879–7.843	0.084	0.650	0.194–2.115	0.474
Glucose	0.889	0.709–1.068	0.224	0.984	0.862–1.114	0.804	1.030	0.842–1.259	0.767
APACHE II	1.122	1.109–1.253	0.018	1.234	1.115–1.414	0.000	1.121	1.027–1.242	0.009
SOFA	1.221	1.040–1.480	0.023	1.158	1.023–1.326	0.025	1.219	1.047–1.456	0.017
Scr	1.012	1.004–1.022	0.006	1.007	1.001–1.013	0.012	0.997	0.991–1.001	0.182
ALT	1.001	0.991–1.008	0.840	0.998	0.991–1.003	0.484	1.001	0.999–1.004	0.113
BNP	0.649	0.236–1.364	0.282	1.780	1.133–2.950	0.012	2.165	1.359–3.858	0.003
hsTnT	0.842	0.227–1.931	0.731	1.305	0.809–2.089	0.262	3.785	1.21–18.38	0.015
PCT	0.983	0.927–1.024	0.454	0.998	0.972–1.020	0.848	1.000	0.975–1.024	0.988
CRP	1.008	0.992–1.022	0.285	1.013	1.004–1.022	0.004	1.009	0.999–1.019	0.078
Lactic acid	1.014	0.841–1.158	0.851	0.985	0.788–1.178	0.880	1.113	0.886–1.415	0.351
APN	0.389	0.181–0.632	0.000	0.687	0.540–0.840	0.000	0.882	0.735–1.036	0.129

Odds ratios, 95% CIs, and p values were obtained by univariate logistic regression analysis. BMI, Body Mass Index; CAD, coronary artery disease; CKD, chronic kidney disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; Scr, serum creatinine; ALT, alanine transaminase; BNP, brain natriuretic; hsTnT, high-sensitivity troponin T; PCT, procalcitonin; CRP, C reactive protein; APN, adiponectin. OR, odds ratio.

We then performed multivariate regression analyses of these parameters that were significantly different. Among them, only APN (OR = 0.296, 95%CI = 0.079–0.599, p = 0.011), and APACHE II (OR = 1.24, 95%CI = 1.072–1.508, p = 0.010) in < 60 years group, APN (OR = 0.651, 95%CI = 0.411–0.907, p = 0.027), APACHE II (OR = 1.24, 95%CI = 1.072–1.508, p = 0.010) and BNP level (OR = 3.69, 95%CI = 1.656–11.17, p = 0.005) in 60–80 years group showed a significant association with 28-day mortality, independent of the other parameters (Table 4).

Table 4
Multivariate logistic regression analysis of factors associated with 28-day mortality in different age stratification.

Varible	< 60 years			60-80years			> 80 years		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
APACHE II	1.24	1.072–1.508	0.010	1.282	1.101–1.585	0.006	1.186	1.048–1.383	0.014
SOFA	1.037	0.817–1.316	0.758	1.200	0.993–1.503	0.076			
Scr				1.009	1.000-1.021	0.069			
BNP				3.690	1.656–11.17	0.005	1.957	1.167–3.646	0.017
CRP				1.002	0.988–1.016	0.748			
APN	0.296	0.079–0.599	0.011	0.651	0.411–0.907	0.027			

Odds ratios, 95% CIs, and p values were obtained by multivariate logistic regression analysis. BMI, Body Mass Index; CAD, coronary artery disease; CKD, chronic kidney disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; Scr, serum creatinine; ALT, alanine transaminase; BNP, brain natriuretic; hsTnT, high-sensitivity troponin T; PCT, procalcitonin; CRP, C reactive protein; APN, adiponectin. OR, odds ratio.

Finally, we performed ROC curve analyses of APN levels to assess the power of predicting 28-day mortality in three group. The AUC values tended to decrease with increasing age, and the sensitivity and specificity of APN for prediction of sepsis-related mortality tended to decrease with age. And in the elderly patients, there was no significant prediction for the mortality. In middle-aged and old patients, APN had

the great discriminative ability (AUC = 0.872 and AUC = 0.774), and an APN cutoff value of 3.355 and 7.985 μg/ml respectively predicted mortality with 88.89% and 83.33% sensitivity, 87.5% and 62.75% specificity (Table 5, Fig. 4).

Table 5
ROC analysis of plasma APN levels for 28-day mortality prediction in septic patients of different ages.

Patients with sepsis	Cutoff value	AUC (95% CI)	Sensitivity	Specificity	p
< 60 years	3.355	0.872 (0.759–0.983)	88.89	87.50	0.0004
60–80 years	7.985	0.774 (0.658–0.890)	83.33	62.75	0.0006

The cutoff value was obtained by ROC curve analysis. APN, adiponectin; AUC, area under the curve; CI, confidence interval; ROC, Receiver operating characteristic.

Discussion

In the present study, we demonstrated that plasma APN levels were significantly lower in patients with sepsis compared with critically ill patients without sepsis. In both control and sepsis patients, plasma APN levels are positively correlated with age. Mortality was considerably higher among patients aged ≥ 60 years compared with middle-age patients (< 60 years). Patients aged ≥ 80 years had significantly higher mortality compared with younger patients. However, APN levels were associated with 28-day mortality in patients aged < 80 years, reflected by the AUC. Lower APN levels were associated with a higher mortality among the patients aged < 80 years, suggesting the potential role of APN in 28-day mortality in sepsis patients younger than 80 years. And there were no significant findings of association of APN and 28-day mortality among the elderly patients aged ≥ 80 years.

APN exerts an anti-inflammatory effect, and recent observations point to a potential role of APN in acute inflammatory diseases. Although the exact mechanism of how this anti-inflammatory protein functions remains to be elucidated in the context of sepsis, several studies support a beneficial role for APN as in the modulation of systemic inflammation in animal models[18–21]. APN exerts this anti-inflammatory effect by several mechanisms, including direct actions on inflammatory cells and interaction with tumor necrosis factor-alpha (TNF-α)[22]. In septic patients, early data suggest that plasma levels of APN are decreased. Whether this is a result of the disease process itself or whether patients with lower levels of this hormone are more susceptible to develop a critical illness has not yet been described[22]. Soares et al. found that adipose cells are highly sensitive to oxidative stress, with subsequent decreased APN secretion and increased lactate producing, which seen in septic patients[23]. Similar to these findings, our previous studies also found that patients with sepsis showed significant lower plasma APN levels. The same results were obtained in the present study.

The present data indicated that patients with sepsis had lower APN levels compared with the control group, and low APN levels were associated with a greater severity of sepsis. In contrast to our results, however, previous studies of sepsis patients reported either increased or similar levels of APN compared

with controls[24, 25]. These discrepancies may be attributable to differences in the studies' objectives, the patients' sepsis stages, and other confounding factors. In Hillenbrand et al[26], patients were stratified based on sepsis stage, and patient cohorts were significantly older and had a considerably higher proportion of male subjects compared with controls. Moreover, in some studies, diabetic patients and patients who received glucocorticoids were not excluded from the study. All of these factors may have an impact on adipokine levels.

Several studies have described correlation between the survival of sepsis patients and APN levels. It was reported that APN levels were more predictive than all other factors that were studied in predicting 28-day survival, including APACHE II score[12, 24]. Hillenbrand et al. found that plasma adipokine levels were considerably altered in severe sepsis or septic shock, with higher proinflammatory adipokine levels and lower anti-inflammatory factor levels[26]. In the present study, the multivariate regression analysis and ROC curve analysis showed that 28-day mortality was significant correlated with APN levels in septic patients aged < 80 years.

A large observational cohort of severely septic ICU and non-ICU patients in the Unites States reported higher mortality among patients aged > 85 years compared with their general study population[27]. Bagshaw et al[1], concluded that age ≥ 80 years, regardless of ICU admission diagnosis, was associated with higher ICU and hospital mortality compared with younger patients. It was also reported that for ICU patients with intra-abdominal infection, age > 60 years was associated with mortality, and patients aged ≥ 80 years had the worst prognosis[28]. Likewise, in the present study, we found that mortality in septic patients increased with age, and septic patients aged ≥ 80years had significantly higher mortality. The limited studies reported that there are many factors contributing to the increase in mortality among the elderly, such as physiological alterations in immunity, chronic underlying diseases, malnutrition, and frailty[28].

As a protective factor of sepsis, the relationship between the APN levels and age in patients with sepsis were further examined in our study. Previous studies have reported that plasma APN levels are increased in elderly individuals[13–15, 29]. Obata et al. found that serum APN levels were significantly and positively associated with age in healthy subjects and in patients with diabetes, and the association was independent of renal function, body fat status, glucose metabolism and lipid profiles[17]. Recently, Sebastiani et al[29]. assessed 38 age-related circulating biomarkers in approximately 5,000 healthy, older adults of the long-life family study, APN and NT-proBNP showed similar positive correlation coefficients with age. In the present study, plasma APN levels were positively correlating with age in patients with sepsis. To the best of our knowledge, this is the first study to examine this association. The pathogenesis of the age-related increase in plasma APN levels is unclear. Several studies have suggested that the age-related increase in serum adiponectin levels is associated with deterioration in renal function[14], but other studies have found no such association[16].

Several studies have been found that APN level increased in patients with chronic kidney disease[30, 31], type 1 diabetes[32, 33], and congestive heart failure[34], however, hypoadiponectinemia is still an

independent risk factor because these patients also show progression of arteriosclerosis. The age-related increase in plasma APN levels also appears to be paradoxical that high plasma APN levels in the elderly might not have numerous beneficial effects because atherosclerosis is advanced with age[35]. The paradoxical phenomenon also found in our study that age-related mortality and APN levels. In order to validate the protection of APN, we further examined the association between APN and mortality in three age stratification respectively. Just as we expected, 28-day mortality was significant correlated with APN levels in septic patients aged < 80 years, however, no significant relationship was found in the elderly patients. Immense epidemiological evidence also supports the paradoxical relationship between high APN levels and poor outcome in cardiovascular and geriatric conditions. Arai et al investigated the association between a set of adipokines and all-cause mortality in a prospective cohort study of 252 centenarians, and plasma APN levels were not associated with mortality in the total sample or in the lower-BMI group[36]. Furthermore, in a middle-aged/older cohort, increased levels of total APN were significantly associated with higher all-cause mortality in age- and sex- adjusted analyses among subjects with, but not without, prevalent cardiovascular diseases[37]. One of the interpretations for the paradoxical phenomenon was that the high circulating APN levels in elderly patients are thought to be due to APN resistance coupled with reduced APN receptor levels in skeletal muscle[38, 39]. APN resistance appear to increase with the age and are known to be associated with increasing mortality. Aging-associated weight loss and sarcopenia which are major determinants of mortality in older adults and are associated with increased APN levels might be the other underlying factor[40]. Our present study did not show the significant relationship between the high APN level and mortality in elderly patients. Further research is necessary to define the role of APN on elderly patients in sepsis and the underlying mechanisms.

A limitation of the present study is that the this was a single-center study with a relatively small sample size, hence, it may be unclear if results could be generalized to other populations of critically ill septic patients. Also, we do not have a complete longitudinal data with plasma determinations at multiple time points. However, it is extremely difficult to obtain an adequately powered longitudinal study with no missing data. Third, there may also have been a selection bias because there were some missing data, especially the elderly patients due to different reasons. Fourth, the present study was not designed to provide mechanistic insights into the role of APN in patients with sepsis. Lager multi-center trials are needed to determine the role of APN in sepsis.

Materials And Methods

Population and protocol

The retrospective study was conducted in the intensive care unit (ICU) of China-Japan Friendship Hospital between January 2016 and January 2019. The study protocol was approved by the ethic review board of China-Japan Friendship Hospital. Informed consent was obtained from all the enrolled patients or their family when some patients had been mechanically ventilated and/or had altered mental status.

A total of 173 patients (> 18 years of age) with a preliminary diagnosis of sepsis who were admitted to the ICU for longer than 48h were included in the present study. Sepsis was defined according to consensus international guidelines as life-threatening organ dysfunction that is caused by dysregulation of the host response to infection. Organ dysfunction was defined as an acute change in the total Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points consequent to the infection[41]. The exclusion criteria were: pregnancy, history of malignancy (solid organ or hematopoietic system), immunosuppression from causes other than sepsis (e.g., post-organ transplant and ongoing chemotherapy). The 57 postoperative patients without the diagnosis of sepsis were included in the control group.

Data Collection

Baseline clinical and laboratory characteristics included age, sex, past illness, and blood chemistry (e.g., brain natriuretic peptide [BNP], C-reactive protein [CRP], procalcitonin [PCT], serum creatinine [Scr], alanine transaminase [ALT], high-sensitivity troponin T [hsTnT], and arterial blood gas) were measured using standard clinical methods at China-Japan Friendship Hospital. The data were collected at the time of a diagnosis of sepsis or upon admission. Disease severity was assessed by SOFA scores and Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores on the day of diagnosis.

Plasma APN levels and biochemical assays

Blood samples were obtained on the day of admission or sepsis diagnosis and centrifuged at 1000×g for 15 min at 4°C within 30 min of collection. Plasma was withdrawn and stored at -80°C until analysis. Plasma APN levels were measured using an enzyme-linked immunosorbent assay (ELISA) for human APN (human APN ELISA kit; R&D Systems, Emeryville, CA, USA). Optical density was measured at 450nm. The limit of APN detection was 0.891ng/ml according to the manufacturer's instructions.

Statistical analysis

The data were analyzed using SPSS 23.0 software (IBM, Armonk, NY, USA) and Prism 7.0 software (Graphpad, San Diego, CA, USA). The distribution of variables was tested for normality with the using of the Klomogorov-Smirnov (K-S) method. Descriptive data are presented at mean ± standard deviation or medians (25th-75th percentile) for continuous variables or as number of patients and percentage for categorical variables. The distribution of variables was compared between control subjects and sepsis patients, using unpaired *t*-tests for normality distributed variables, or the Mann-Whitney *U*-test for not-normality distributed variables. Patients with sepsis were divided into three age groups (< 60, 60–80, ≥ 80 years). Variables were compared between each age group using analysis of variance (AVONA) for normality or Kruskal-Wallis H test for non-normality variables. Pearson or Spearman correlation coefficients were calculated to test association between APN and individuals' parameters, including age for normality or non-normality variables. Survival curves for middle-aged, old and elderly sepsis patients

were prepared by the Kaplan-Meier method. Univariate and multivariate logistic regression analyses were performed to identify risk factors for sepsis-related mortality, and results were reported as odds ratios (OR) and 95% confidence intervals (CI). Receiver operating characteristic (ROC) curves were generated to determine specificity and sensitivity for predicting the28-day mortality in sepsis. Two-tailed values of $p < 0.05$ were considered statistically significant.

Conclusions

In conclusion, we found a significant positive association between plasma APN levels and age in septic patients. And low circulating levels of APN were associated with a higher risk of death in septic patients aged < 80years. APN levels were an independent predictor of mortality in our model < 80years. The association between APN and mortality in sepsis patients aged > 80years were not significantly found. On the basis of these results, we consider that clinicians should take into account age-related changes in plasma APN levels when interpreting a patient's plasma APN level in clinical practice.

Declarations

Acknowledgement

None.

Author's contributions

WH, WYN and DJ contributed to design the conception and design of the study. WH, MM and LC participated in acquisition and analysis of data for the study. WH, MM and GYX drafted the work. ZSS was responsible for statistics data management, analysis and interpretation and reviewed the manuscript. All authors collaborated to interpret data and revise the work critically for important intellectual consent. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author on the reasonable request.

Ethical Approval

The research ethics committee of the China-Japan Friendship Hospital, Beijing, China approved the studies, and all participants provided a written informed consent.

Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Figures

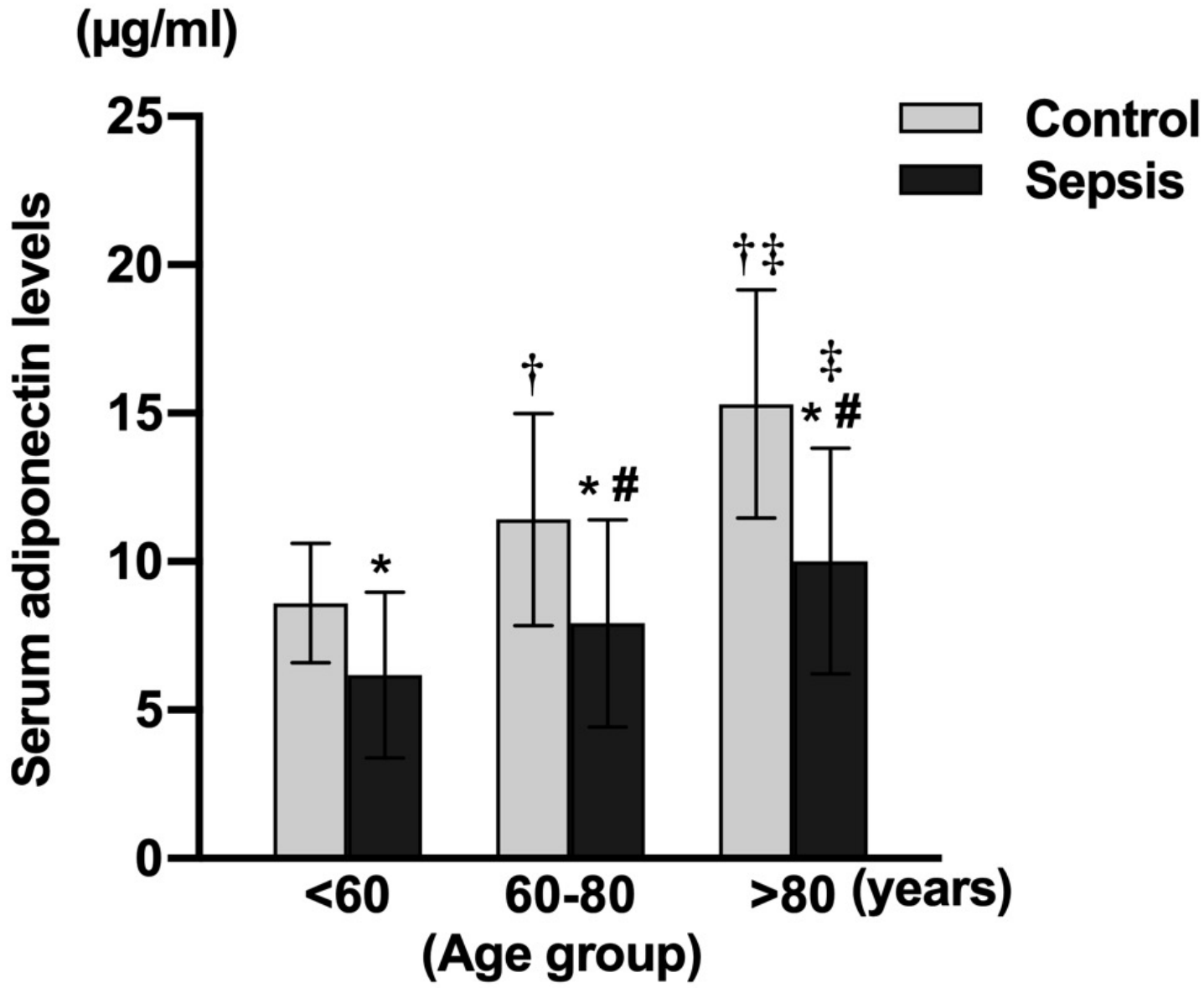

Figure 1

The plasma adiponectin levels in each age group in control and sepsis group. * p<0.05 versus control group in each age group. # p<0.05 versus <60 group in sepsis patients, † p<0.05 versus <60 group in controls, ‡ p<0.05 versus 60-80 group both in control and sepsis patients.

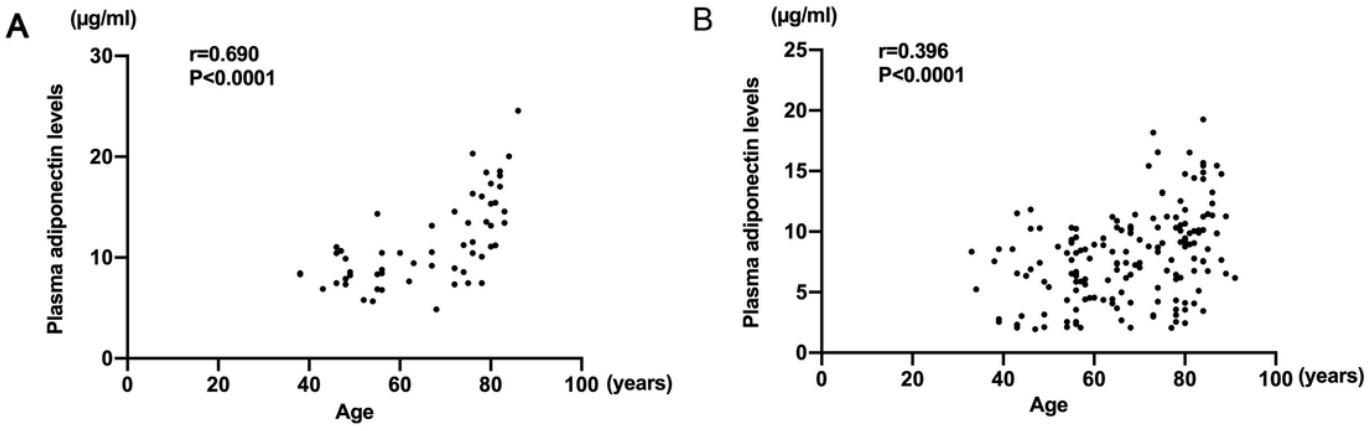

Figure 2

The positive association between age and adiponectin level in control group (A) and sepsis group (B). Correlation between the plasma APN level and age was confirmed by values of r=0.690, p<0.0001 and r=0.396, p<0.0001 in control and sepsis group respectively.

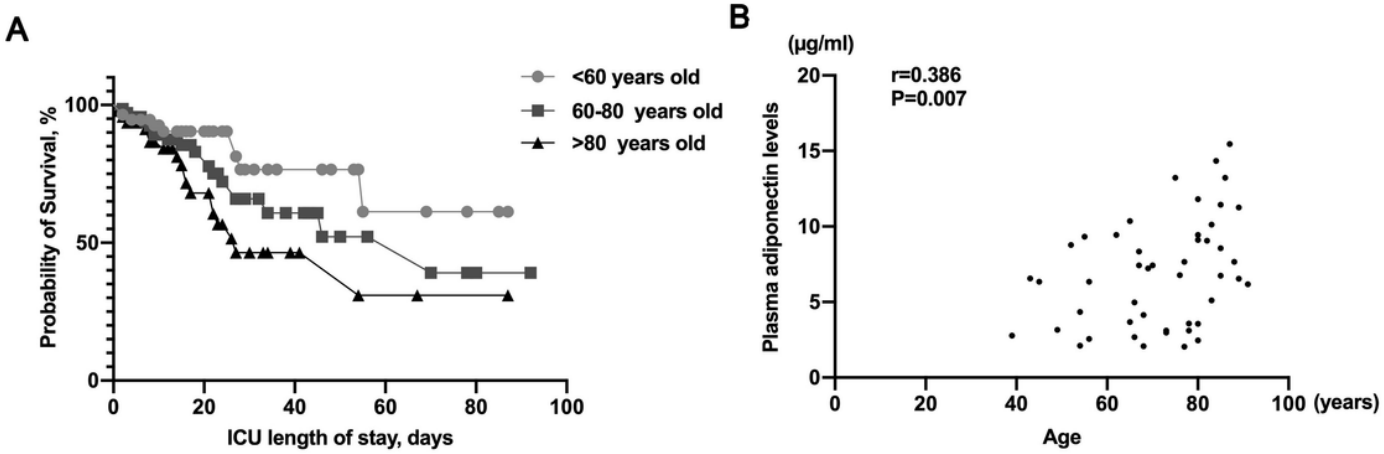

Figure 3

A. Survival curves for middle-aged, old and elderly patients with sepsis. Survival curves were generated by Kaplan-Meier method. B. The positive association between age and adiponectin level in deceased patients. Correlation between the plasma APN level and age was confirmed by values of r=0.386 and p<0.0001.

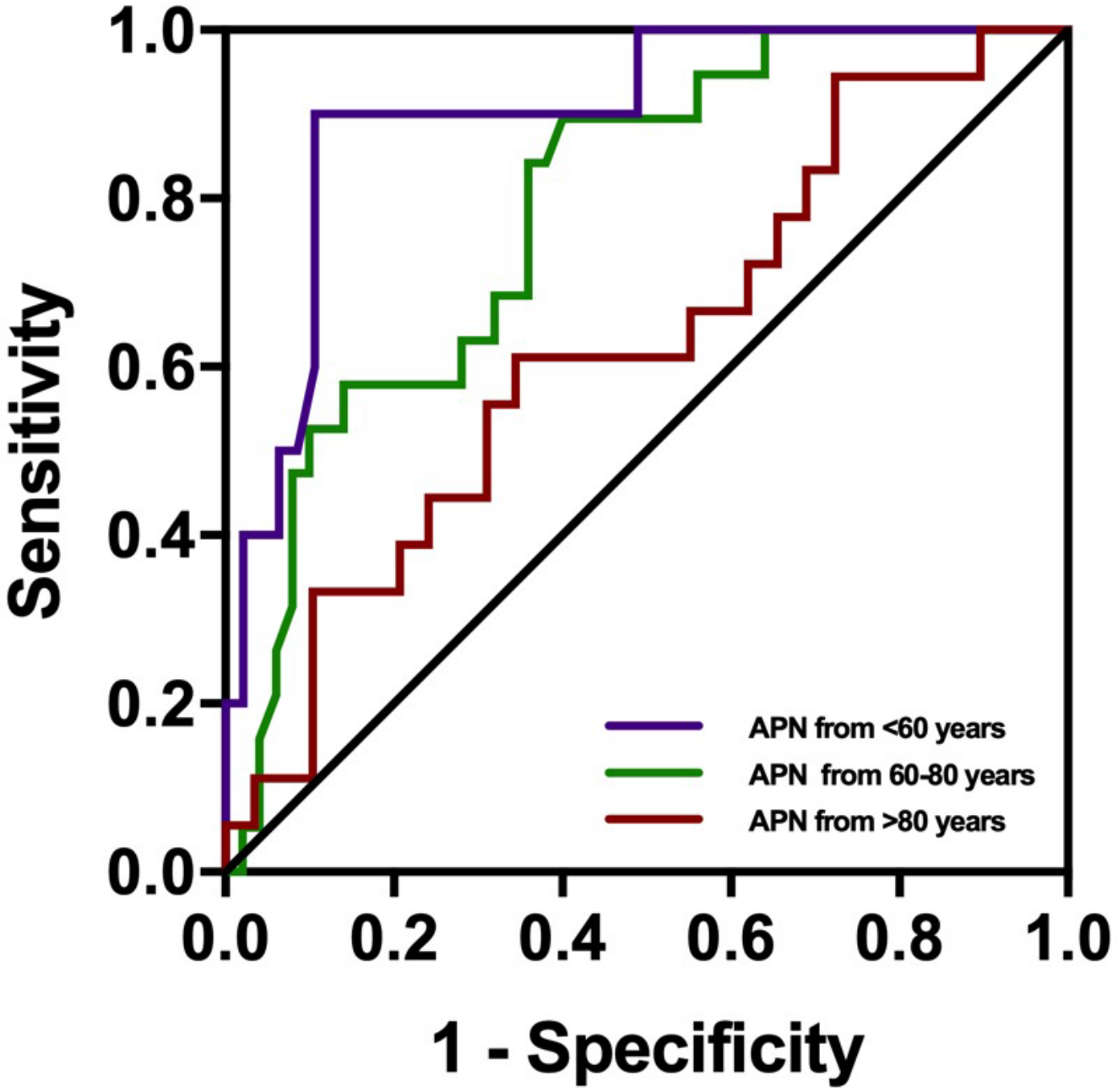

Figure 4

Receiver operating characteristic curve analysis of the ability of adiponectin to predict 28-day mortality in septic patients at the age <60 years, 60-80 years, and >80 years.