ORIGINAL ARTICLE

Adrenomedullin and Its Possible Role in Improved Survival in Female Patients with Sepsis: A Study in the South East Asian Region

Mradul K Daga[1], Lalit Kumar[2], Govind Mawari[3], Naresh Kumar[4], Shashank Singh[5], Tarun Kumar Mishra[6]

Abstract

Aims and objectives: Serum adrenomedullin (ADM) as a prognostic biomarker to study the gender-related differences in mortality pattern and its correlation with the sequential organ failure assessment (SOFA) and acute physiologic assessment and chronic health evaluation II (APACHE II) scores in patients of sepsis.

Measurements and main results: Eighty patients of sepsis of which 36 were males and 44 were females, were taken in the study as per sepsis III guidelines. They were followed up for a period of 28 days. Serum ADM was measured on day 1 and day 5. The endpoint was mortality or survival at day 28 after admission. The death rate among males was higher, with 23 of the total 36 (63.89%) patients having died when compared with females in which 25 patients out of 44 (56.82%) had died. The observed mortality rates correlated well with average APACHE II scores. The average APACHE II score was slightly higher in males (29 ± 8.97) when compared with females (27.02 ± 8.69). Similarly, day 1 SOFA and mean SOFA values were higher in males (10.22 ± 5.36) and (10.73 ± 6.01) when compared with females (8.27 ± 4.79) and (8.89 ± 5.6), respectively. Males despite having higher mortality rates, higher APACHE II, SOFA, and mean SOFA values were still having less mean levels of serum ADM (454.40 ± 81.13 pg/mL) when compared with females (479.62 ± 126.97 pg/mL).

Conclusion: Adrenomedullin is a protective neurohormone with antibacterial and anti-inflammatory properties. It is elevated in all patients with sepsis but the rise is more so in the female when compared with males. Higher ADM levels in females may suggest the protective effect of ADM as a part of the general protective neurohormonal stress response, which may explain the low death rate in females in sepsis.

Keywords: Adrenomedullin, Mortality, Sepsis, Septic shock.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23672

Introduction

Sepsis is one of the most complex syndromes in medicine and it is one of the leading causes of mortality in critically ill patients to the tune of 20–40% in intensive care unit (ICU) with sepsis and 50% in septic shock.[1] It has long been thought that males have higher death rates in sepsis.[2–5] Neurohormonal and immunological responses to the condition may be a possible explanation for these gender-related difference in the outcome of patients with the female having a better profile.[5]

There are many biomarkers available to predict the course of this disease. Procalcitonin and lactate are the most extensively studied biomarkers. Adrenomedullin (ADM) is a molecule that was first isolated in 1993 from a pheochromocytoma.[6] Adrenomedullin has anti-inflammatory, bactericidal, positive ionotropic, and vasodilatory action (ADM may function as a hormone in circulation control). Adrenomedullin may also promote angiogenesis. The levels of ADM are high in patients with sepsis and its levels can predict the risk of mortality as well as the development of septic shock.[7–9]

Little is known about gender and ethnicity related difference in ADM. In a study conducted in Japan on normal persons who came for regular health check-ups, the average ADM levels were less in females when compared with males.[10]

In this study, we analyzed the differences between male and female levels of ADM in critical patients of sepsis. To our surprise, the average ADM levels were more in females suggesting that the neurohormonal stress response of female patients is better than males in sepsis, probably accounting the for less mortality rate observed in them.

[1–5]Department of Medicine, Maulana Azad Medical College, New Delhi, India

[6]Department of Biochemistry, Maulana Azad Medical College, New Delhi, India

Corresponding Author: Mradul K Daga, Department of Medicine, Maulana Azad Medical College, New Delhi, India, Phone: +91 9990092732, e-mail: drmraduldaga@gmail.com

How to cite this article: Daga MK, Kumar L, Mawari G, Kumar N, Singh S, Mishra TK. Adrenomedullin and Its Possible Role in Improved Survival in Female Patients with Sepsis: A Study in the South East Asian Region. Indian J Crit Care Med 2020;24(12):1180–1184.

Source of support: Nil

Conflict of interest: None

Materials and Methods

The study was approved by the Institutional Ethical Committee and written informed consent was obtained from all patients before their inclusion in this study.

Based on previous literature research and keeping a level of significance at 95% ($\alpha = 0.05$) and power of the study (1−β) at 80%, with an absolute error of 10% as acceptable, the minimum sample size calculated was 400 (using Epi info version 6.0, CDC, Atlanta, and PS Software). The sample was calculated by using the formula:

$$3.84\, P\,(1-P)\,/\,n\,2$$

where P is the prevalence of mortality in sepsis taken as 0.08 (8%) and n is the allowable error taken as 0.05.

However, due to time constraints, 80 patients of sepsis (according to sepsis guidelines, 2014) who presented to the medicine department emergency of Lok Nayak Hospital, attached to Maulana Azad Medical College, New Delhi between May 16 and February 17 were included in the study and followed through a period of 4 weeks. Both sexes were divided into two categories based on the follow-up of 28 days, respectively, as survivors and non-survivors. Patients enrolled in the study were subjected to complete history and clinical examination, all routine blood biochemistry along with chest X-ray and other appropriate imaging, culture from suspected sites of infection (and/or automated blood culture), measurement of serum ADM levels on day 01 and day 5 by ELISA method was done. The acute physiologic assessment and chronic health evaluation II (APACHE II) score was calculated within 24 hours of admission. The sequential organ failure assessment (SOFA) score was calculated at admission and every alternate day till day 7 or till the expiry of the patient whichever was earlier. The mean SOFA score was calculated as the average of these SOFA scores.

Exclusion Criteria

Patients with a history of anaphylaxis, adrenal insufficiency, trauma, burn, and patients in whom physiological conditions or preexisting illness affecting ADM levels were excluded from the study.

Statistical Analysis

The data were analyzed using SPSS/22.0 software. The description of quantitative variables was performed using the mean, standard deviation (SD), median, and quartiles. A p value of <0.05 was considered significant. The correlation between variables was performed using the Pearson correlation coefficient, independent t-test, biserial analysis, and linear correlation graphs. A p value of <0.05 was considered significant.

Results and Analysis

The study involved 80 patients of sepsis of which 36 were males and 44 were females (Table 1). The mean age of the patients in the study was 52.26 ± 17.17 years with a range of 15–85 years.

Respiratory (43.75%) and urinary tract (30%) were the most common sites of infection, followed by abdominal infection (10%), meningitis (11.25%), soft tissue abscess, and cellulitis (5%). The most common infection in males was respiratory tract infection (20/36 = 55.56%). This was also the most common cause of death-causing 14 of the total 23 deaths in males. The most common infection among the female subset was that of the urinary tract in 21 (47.72%) patients. Urinary tract infection was also the most common cause of death in females causing 13 of the total 25 (52%) deaths reported in the group. Out of the 80 patients studied, 38 (47.5%) died within the first week of their illness while the total number of deaths was 48 (60%) by day 28.

The death rate among males was higher, with 23 of the total 36 (63.89%) patients having died when compared with females in which 25 patients out of 44 (56.82%) had died. Of particular note was the first-week mortality pattern. Nineteen of 36 males studied (52.78%) had died within the first week of their illness. In females, the death rate in the first week was less with 19 deaths out of 44 patients (43.18%). The outcome course differed between the two genders from the beginning of illness with males at a statistical disadvantage. It was also seen that a larger chunk of male deaths, 19 of the total 23 death in males (82.61%) had occurred in the first week when compared with females with 19 of the total 25 deaths in them (76%) in the first week of illness.

Ten out of the 29 (34.48%) patients who had APACHE II scores of 21–30 died whereas those with a score of 31–40 had 78.25% mortality. None of the patients having an APACHE II score of >34 survived in our study. The mean of the APACHE II scores for the patient who survived till day 28 was much lower in the survivor group (23.095 ± 6.461) when compared with the non-survivor group (33.237 ± 8.022) (p value < 0.001). Those who died within the first week of their illness had slightly higher levels of APACHE II score (33.237 ± 8.022) when compared with patients who died overall during their hospital stay (31.458 ± 8.310) (p value < 0.001). Similarly, the mean day 1 SOFA scores among the non-survivors was (11.40 ± 4.9) higher than the survivors (5.78 ± 3.27) (p value < 0.001).

Table 1: Baseline characteristics of the population

Study variable	*Total population*	*Male*	*Female*
Number of patients (*n*)	80	36	44
Average age in years	52.26 ± 17.17 (range = 15–85 years)	55.78 ± 16.26	49.32 ± 17.54
Most common site of infection	Respiratory tract 35 (43.75%)	Respiratory tract 21 (47.72%)	Urinary tract 20/36 = 55.56%
Day 7 mortality			
Survivors	42 (52.5%)	17 (47.22%)	25 (56.81%)
Non-survivors	38 (47.5%)	19 (52.78%)	19 (43.18%)
Day 28/overall outcome			
Survivors	32 (40%)	13 (36.11%)	19 (43.18%)
Non-survivors	48 (60%)	23 (63.89%)	25 (56.82%)
APACHE II score on day 1 and day 28 outcome			
Survivors	22.59 ± 6.70	24.54 ± 6.84	21.26 ± 6.44
Non-survivors	31.46 ± 8.31	31.52 ± 9.17	31.4 ± 7.62
SOFA score on day 1 and day 28 mortality			
Survivors	5.78 ± 3.27	5.92 ± 2.9	5.68 ± 3.58
Non-survivors	11.40 ± 4.9	12.65 ± 4.89	10.24 ± 4.72
Mean SOFA score and day 28 mortality			
Survivors	3.91 ± 1.97	3.923 ± 2.02	3.91 ± 2.02
Non-survivors	13.59 ± 4.03	14.58 ± 3.52	12.69 ± 4.32

APACHE II, acute physiologic assessment and chronic health evaluation II; SOFA, sequential organ failure assessment

Mean SOFA score, calculated as the average of SOFA scores on day 1, 3, 5, and 7 was significantly lower in the patients who survived till the fourth week of admission (3.91 ± 1.97) compared with the non-survivor group (13.59 ± 4.03) (*p* value of <0.001). Again patients who died within the first week of illness had slightly higher mean SOFA scores of (14.86 ± 3.22) than the survivors (13.59 ± 4.03) (*p* value < 0.001). APACHE II, day 1 SOFA, and mean SOFA, all were effective in predicting outcome with mean SOFA score most closely related to the outcome followed by APACHE II and finally SOFA (*p* value < 0.001). Average APACHE II scores were slightly higher in males (29 ± 8.97) when compared with females (27.02 ± 8.69). Similarly, day 1 SOFA and mean SOFA values were higher in males (10.22 ± 5.36) and (10.73 ± 6.01) when compared with females (8.27 ± 4.79) and (8.89 ± 5.6), respectively.

Serum Adrenomedullin

The serum ADM on day 1 was elevated in all patients of sepsis. When all patients were seen together, the average ADM levels were more in those who died of their illness (495.27 ± 103.98 pg/mL in non-survivors vs 427.78 ± 104.83 pg/mL in the overall survivor (*p* value 0.006). Similarly, serum ADM levels on day 5 were 201.3 ± 73 and 233.32 ± 92.33 pg/mL in the overall survivor and non-survivor group, respectively (*p* value 0.02) (Fig. 1). The difference in the mean ADM levels on day 1 and day 5 can be explained by the fact that ADM levels correspond to the initial hit in sepsis, hence higher levels on day 1 when compared with day 5. There was an unfavorable outcome in patients in whom ADM levels were more on day 5 than day 1. Serum ADM levels on both day 1 and day 5 could predict the overall outcome in patients of sepsis. This preliminary data gave the impression that the higher the ADM levels higher the death rates. However, when the two-gender subgroups were analyzed, males despite having higher mortality rates (Table 2), higher APACHE II, SOFA, and mean SOFA were still having less mean levels of serum ADM (454.40 ± 81.13 pg/mL) when compared with females (479.62 ± 126.97 pg/mL). This was in sharp contrast to what was expected and was also the most important observation of this study which suggested that indeed there are differences in neurohormonal response between the two genders in sepsis, as reflected by lower ADM values in males. This might be a possible explanation for higher mortality in the males in sepsis.

Discussion

Sepsis is a complex syndrome with wide variations in its presentations. Sepsis is a medical emergency and prognostication of these patients is extremely important.[11] In our study, we saw that mortality was high with 48 out the 80 patients (60%) died within 28 days (Table 1). It was also observed that while male patients had a death rate of 63.82%, females had fewer chances of dying with a death rate of 56.82%. The most common cause of sepsis in females was an infection in the urinary tract, whereas it was the respiratory tract in males. This becomes an important observation because females are the deprived gender in society and less likely to receive adequate healthcare resources on time, yet post-hospitalization they fared better than males. These differences in mortality patterns have been observed in both animal and human studies and many possible explanations have been given over time to explain these differences. Neurohormonal differences between the two sexes and immune dysfunction in males are among the two best possible explanations to date.

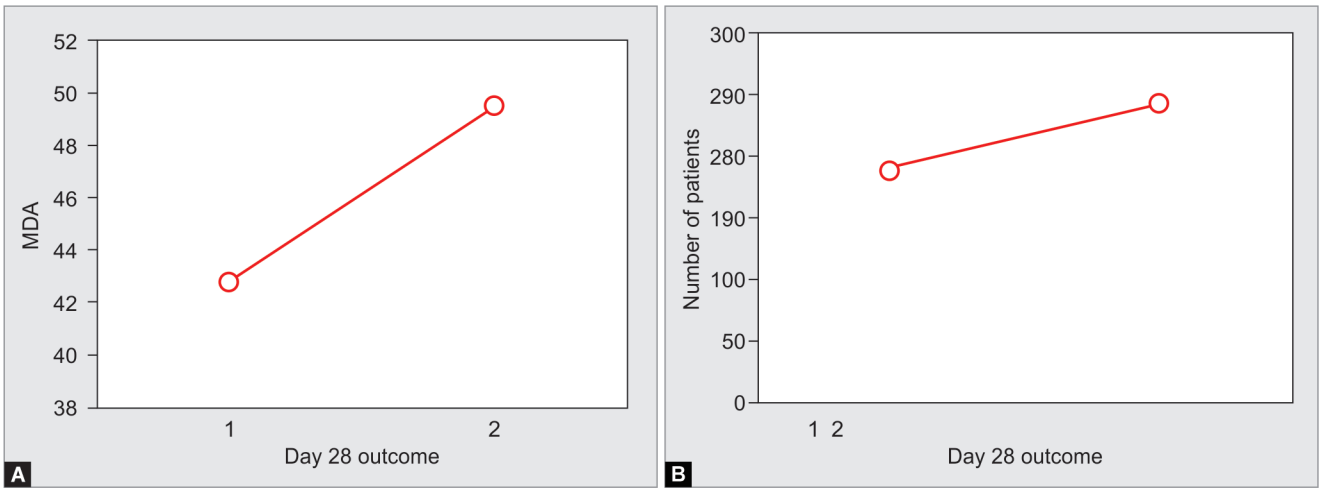
Many scoring systems have been used for prognostication in the past. The APACHE II and SOFA scoring systems are the most widely used scoring systems. In our study, the APACHE II, SOFA, and mean SOFA all were higher in the male population and thus accounting for higher death rates in males (Table 2).

Although the scoring systems will continue to be superior to biomarkers in sepsis, biomarkers are important because they reflect the early hit in sepsis when the internal milieu of the body just begins to change, whereas scoring systems are based on

Table 2: Sex-related differences in sepsis

Population characteristics	*Male (n = 36)*	*Female (n = 44)*
Avg day 1 APACHE II	29 ± 8.97	27.02 ± 8.69
Avg day 1 SOFA	10.22 ± 5.36	8.27 ± 4.79
Avg mean SOFA	10.73 ± 6.01	8.89 ± 5.61
Avg day 1 ADM values in pg/mL	454.40 ± 81.13	479.62 ± 126.98
Percentage mortality at day 28	63.89	56.82

ADM, adrenomedullin; APACHE II, acute physiologic assessment and chronic health evaluation II; SOFA, sequential organ failure assessment



Figs 1A and B: Difference in serum adrenomedullin (ADM) levels on day 1 and day 5 between survivors and non-survivors with respect to final day 28 outcome. Both day 1 ADM (ADM1) and day 5 ADM (ADM5) levels were higher in non-survivors suggesting ADM as a possible neurohome in sepsis

organ dysfunction, and by that time the hit is already widespread. Thus, biomarkers continue to be a field of active research. Many biomarkers have established their efficacy in sepsis. Procalcitonin and lactate are the most extensively studied till now. In our study, we studied the neurohormone ADM levels as a biomarker and see if it could explain these differences in sepsis. Serum ADM levels were increased in all patients of sepsis, and day 1 and day 5 levels could effectively predict long-term mortality in patients of sepsis (Table 3). Mean serum ADM on day 1 in the survivor group at the fourth week was 427.78 ± 104.83 pg/mL compared with that in the non-survivor group 495.27 ± 103.98 pg/mL. It was statistically significant (*p* value 0.006). Hence, serum ADM levels on day 1 could effectively predict the long-term mortality in patients of sepsis. Tamer and Bassem also carried out a similar study in 2016 and they concluded that ADM values at day 1 of admission can be used to predict outcome.[9] Adrenomedullin levels could predict day 28 mortality as well as the need for ionotropic support in the future with a sensitivity of 100% and specificity of 93.8% in their study. Marino et al. studied 134 patients of sepsis admitted in medical emergency and plasma ADM levels were obtained daily on admission and the next 4 days. The day 28 mortality rate was recorded and it was observed that ADM levels correlated with day 28 outcome and it could also predict those who would develop septic shock in the future.[7] Simon et al. studied 42 patients with sepsis in ICU and 14 patients who developed sepsis after major surgery. Higher ADM levels were associated with increased vasopressor need and mortality at 90 days.[8]

Table 3: Day 1 adrenomedullin levels among patients and percentage mortality in that range

Adrenomedullin in pg/mL	*N*	*Percentage of the total population in that range*	*Day 28 mortality*	*Mortality rate in that range (%)*
≤280	1	1.25	0	0
280.1–320	1	1.25	0	0
320.1–360	8	10	2	25
360.1–400	7	8.75	4	57.14
400.1–440	15	18.75	9	60
440.1–480	16	20	10	62.5
480.1–520	9	11.25	7	77.78
520.1–560	13	16.25	9	69.23
560.1–600	4	5	2	50
600.1–640	2	2.5	1	50
≥640	4	5	4	100

In the present study, the ADM level on day 1 could effectively predict the need for ionotropic use in patients with sepsis. The *p* value of this correlation is 0.001 which is statistically significant. Adrenomedullin levels on day 1 acted as an independent factor to determine the day 28 mortality. Adrenomedullin levels on day 5 could also effectively predict the 28-day mortality of patients with sepsis. The *p* value for this was 0.02, which was statistically significant. (The *p* value for ADM day 1 with 28-day outcome was 0.006 less than the *p* value of 0.02 between ADM 5 and day 28.) It can be said that ADM levels on day 1 are more strongly related to overall outcome than ADM levels on day 5.

When ADM levels were analyzed in males and females subgroups, the result was in sharp contrast to other parameters. While it was seen that the average prognostic score and mortality rates were higher in males yet it was the female gender that had higher average ADM levels. As seen in Table 3, the mortality rates raised initially, reached a peak in the subgroup with initial ADM levels of 480–520 pg/mL, and then started declining in the next three subgroups till a value of 640 pg/mL. Indeed, the numbers of females in these subgroup groups were higher. Adrenomedullin having anti-inflammatory and the antibacterial property was hence protective in females. In the subgroup with initial ADM levels of 640 pg/mL or more, all four of our patients in the study died reflecting the fact that in these patients the initial hit of sepsis was high and so were the counteracting ADM levels (Fig. 2). Reade et al. Also observed that anti-inflammatory cytokines are elevated in a female patient of sepsis however they did not study ADM in their study.

Conclusion and Importance of the Study

The need for a biomarker that addresses the earliest hit in patients of sepsis continues. While scoring systems are giving reliably accurate prognosis estimation, they depend mainly on organ dysfunction by which time the damage may be irreversible. Serum ADM increases in

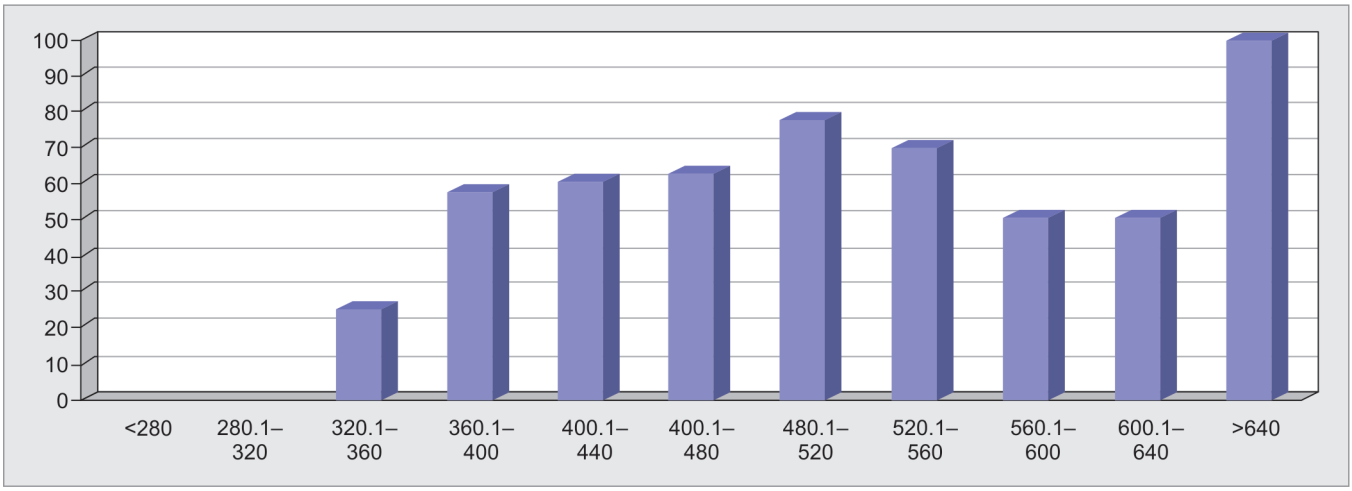


Fig. 2: Mortality rates compared with serum adrenomedullin (ADM) levels on day 1. It can be seen that mortality rises as serum ADM level increases till the 480–520 pg/mL range. However, beyond that mortality stats decreasing suggesting a possible zone of the protective effect of ADM in sepsis. The mortality once again rises when ADM levels reach beyond 640 pg/mL levels suggesting that the disease burden of sepsis was high and the initial hit was high and survival was not possible despite the protective effect

all patients of sepsis and when measured on admission it serves as an early marker of the development of septic shock and mortality.

In our study, we saw that serum ADM levels were correlating well with the outcome of patients. Also, the levels of serum ADM in the female subset were higher than males despite the latter having higher organ dysfunction assessment scores and mortality rates. Hence, this study provides support to the theory that lack of adequate protective neurohormonal response in males may be the explanation for observed higher death rates in them. However, that being said the number of patients in the study is less and more data is needed to make precise statements. Adrenomedullin is just one of the many protective mechanisms in sepsis. A study of a combination of various protective neurohormones and immunological mediators of inflammation may serve our purpose better than relying solely on one biomarker. Whatever be the case due to the increasing burden of sepsis and the world population getting older these neurohormones will enjoy a considerable interest in the future as a marker and as a therapeutic option in sepsis.

Take Home Message

Sepsis is a complex syndrome with unacceptably high mortality rates. The frustration will only increase with the rise in antimicrobial resistance in the future. Yet in nature, females are somehow having better survival rates than their male counterparts when sepsis is the diagnosis. Adrenomedullin, a neurohormone with antibacterial and anti-inflammatory properties, is elevated in all patients with sepsis but more so in the female sex when compared with males. Differences in neurohormones and immunological mechanisms between the two genders may be a possible explanation for this observation of better survival in females.

Declarations

- Ethics approval: This study was conducted only after approval from the institutional ethical committee Maulana Azad Medical College and with the aid of informed consent from all the patient-participants.
- Consent for publication: After the consent, Performa was filled for each subject enlisting his demographic as well as observed parameters. Subjects were also informed about the possibility of publication of study findings.
- Availability of data and material: Data related to the study and its findings are maintained in safe and secured databases without compromising the participant confidentiality.
- Authors' contributions: Mradul K Daga, Naresh Kumar, and TK Mishra supervised the study. Govind Mawari coordinated it. Conducted by Lalit Kumar. Compiled and analyzed by Shashank Singh, Lalit Kumar, and Govind Mawari. MK helped in streamlining the proceedings.

References

1. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Critical Care Medicine 2006;34(2):344–353. DOI: 10.1097/01.CCM.0000194725.48928.3A.
2. Eachempati SR, Hydo L, Barie PS. Gender-based differences in outcome in patients with sepsis. Arch Surg 1999;134(12):1342–1347. DOI: 10.1001/archsurg.134.12.1342.
3. Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. Crit Care 2012;16(3):R92. DOI: 10.1186/CC11355.
4. Kisat M, Villegas CV, Onguti S, Zafar SN, Latif A, Efron DT, et al. Predictors of sepsis in moderately severely injured patients: an analysis of the ational trauma data bank. Surg Infect (Larchmt) 2013;14(1):62–68. DOI: 10.1089/sur.2012.009.
5. Reade MC, Yende S, D'Angelo G, Kong L, Kellum JA, Barnato AE, et al. Differences in immune response may explain lower survival among older men with pneumonia. Crit Care Med 2009;37(5):1655–1662. DOI: 10.1097/CCM.0b013e31819da853.
6. Kitamura K, Kato J, Kawamoto M, Tanaka M, Chino N, Kangawa K, et al. The intermediate form of glycine-extended adrenomedullin is the major circulating molecular form in human plasma. Biochem Biophys Res Commun 1998;244(2):551–555. DOI: 10.1006/bbrc.1998.08310.
7. Marino R, Struck J, Maisel AS, Magrini L, Bergmann A, Di Somma S. Plasma adrenomedullin is associated with short-term mortality and vasopressor requirement in patients admitted with sepsis. Critical Care 2014;18(1):R34. DOI: 10.1186/cc13731.
8. Simon TP, Martin L, Doemming S, Humbs A, Bruells C, Kopp R, et al. Plasma adrenomedullin in critically ill patients with sepsis after major surgery: a pilot study. J Crit Care 2017;38:68–72. DOI: 10.1016/j.jcrc.2016.10.017.
9. Tamer A, Bassem N. Prognostic role of adrenomedullin in sepsis. Int J Adv Res Biol Sci 2016;3(5):136–141.
10. Kawano S, Kawagoe Y, Kuwasako K, Shimamoto S, Igarashi K, Tokashiki M, et al. Gender-related alterations in plasma adrenomedullin level and its correlation with body weight gain. Endocr Connect 2015;4(1):43–49. DOI: 10.1530/EC-14-0131.
11. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. Third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):801–810. DOI: 10.1001/jama.2016.0287.