Sepsis Unmasked: Decoding the Power of Adrenomedullin and Neutrophil to Lymphocyte and Platelet Ratio in sepsis associated Acute Kidney Injury

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Abstract

Background: Acute kidney injury (AKI) in critically ill cases is primarily caused by sepsis. Intrarenal and systemic inflammation play a crucial role in the pathophysiology of Sepsis Associated Acute Kidney Injury (SA-AKI). The neutrophil to lymphocyte and platelet (N/LP) ratio serves as an indirect inflammation marker. Adrenomedullin, a protein belonging to the calcitonin family, has been shown to elevate significantly in cases with sepsis. **Aim of the work:** The goal of the work was to assess the ability of neutrophil to lymphocyte and platelet ratio and plasma Adrenomedullin, at admission, for detection and mortality prediction of SA-AKI cases admitted to an intensive care unit (ICU). **Patients and methods:** This investigation has been carried out on 60 cases admitted to ICU of Kasr Al-Ainy Hospital, Cairo University, diagnosed to have sepsis associated acute kidney injury; of whom 55% had septic shock and 45% had sepsis. **Results:** Mortality among the investigated cases accounted 36.7%. Increased incidence of septic shock, higher, KIDGO staging for renal failure, creatinine level, NLP ratio, plasma Adrenomedullin, need for RRT and lactate at admission and after 48 hours, higher IVC distensibility, length of ICU stay, need for vasopressors, need for mechanical ventilation on admission and after 48 hours and number of organ dysfunction on admission and after 48 hours among non-survived cases with p-value <0.001 correspondingly. There was a statistically significant positive correlation between adrenomedullin level at admission and other parameters including BMI, N/LP ratio on admission and after 48 hrs, Renal function (creatinine) after 48 hrs , Lactate after 48 hrs , Renal function (creatinine) % of change and Lactate % of change with *P*-value <0.05.Also there was statistically significant negative correlation between adrenomedullin and the following; Renal function (creatinine) on admission , Central Venous oxygen Saturation after 48 hrs , and Central Venous oxygen Saturation % of change with *P* -value <0.05. Adrenomedullin level significantly increased at admission and after 48 hours among sepsis associated AKI who had history of diabetes compared to those who did not have diabetes with *P* -value=0.005 and 0.004 respectively. Adrenomedullin after 48 hours significantly associated with increased number organ dysfunction, IVC collapsibility and distensibility at admission and after 48 hours, need for mechanical ventilation, and mortality with *P* -value <0.05. The multivariate logistic regression analysis shows that the most associated factors with mortality were plasma adrenomedullin on admission >77.08, N/LP ratio on admission >3, presence of diabetes, requirement for mechanical ventilation upon admission and KDIGO stage 3. **Conclusions:** our study revealed that both Adrenomedullin and NLP ratio are rapid, inexpensive and emerging biomarkers that may provide significant insights on the pathophysiology, severity, and prognosis of sepsis-associated AKI. These biomarkers may aid in risk stratification, guiding treatment decisions, and monitoring disease progression. Plasma Adrenomedullin and NLP ratio may be reliable predictors of mortality in sepsis-associated acute kidney injury cases. Adrenomedullin and NLP ratio levels were significantly increased in SA-AKI cases, particularly in non-survivors. Biomarkers better to be carried out in supporting a clinical diagnosis. We hope that the utilization of Adrenomedullin and NLP ratio may enhance the management and ameliorate the prognosis of cases with sepsis. **Keywords:** vancomycin- critically ill- renal impairment- dose adjustment-trough concentration.

Introduction

Acute Kidney Injury is defined by a rapid reduction in renal function over a duration of hours to days, leading to the accumulation of creatinine, urea, and other waste products **(Bellomo et al., 2017).** AKI is prevalent in hospitalized cases, with a higher

frequency observed in critically ill cases, where sepsis is the primary etiology of Acute Kidney Injury **(Hoste et al., 2018).** Sepsis is a life-threatening condition characterized by organ failure resulting from a dysregulated host response to infection **(Singer M, et al., 2016).**

The duration of acute kidney injury serves as a predictor for illness severity and outcome **(Brown et al., 2010).** Even transient acute kidney injury is associated with elevated death **(Nejat et al., 2012).** The risk of death in cases with acute kidney injury escalates with the progression of the disease stage **(Joannidis et al., 2009).**

In critically ill cases, the etiology of acute kidney injury is typically multifactorial; still, sepsis is a predominant contributor, accounting for over fifty percent of all sated cases. The etiology of sepsis-induced acute kidney injury involves a multifaceted interplay of elements, including vascular and glomerular thrombosis, inflammation, and shock, differentiating it from non-septic acute kidney injury **(Jacobs et al., 2011).** Consequently, the clinical manifestation, prognosis, and therapeutic responses can vary between septic and non-septic acute kidney injury. SA-AKI is associated with a significantly higher risk of hospital mortality, even after controlling for relevant variables **(Kim et al., 2012).** Cases with septic acute kidney injury exhibit different characteristics compared to those with non-septic acute kidney injury, including elevated severity scores at admission, increased incidence of non-renal organ failure, and a greater necessity for vasopressors and mechanical ventilation **(Gameiro et al., 2020).**

Acute kidney injury is related to prolonged hospitalizations, increased in-hospital mortality, cardiovascular complications, advancement to CKD, and elevated long-term mortality **(Hoste et al., 2018).** Consequently, it is essential to identify predictors of acute kidney injury and mortality to facilitate early prevention, diagnosis, and treatment of this complication.

Recent research has enhanced septic-AKI pathophysiology understanding, characterized by a complicated interaction of microcirculatory, hemodynamic, inflammatory, and immunological mechanisms **(Ma et al., 2019).**

The neutrophil to lymphocyte ratio (N/L ratio) and the neutrophil to lymphocyte and platelet ratio have been related to acute kidney injury in emergency situations, sepsis, contrast-induced acute kidney injury, cardiovascular surgery, and abdominal surgery **(Abu Alfeilat et al., 2018).** These are easily quantifiable, efficient, and low-cost indicators of systemic inflammation that may hold promise for cases with acute kidney injury.

The prognostic ability of N/LP ratio hasn't been formerly assessed in septic-AKI **(Pereira et al., 2017).** Adrenomedullin is a member of the calcitonin gene-related peptide family that, in addition to several endocrine biological activities, induces a specific vasodilation of resistant vessels. Adrenomedullin engages with various complex physiological pathways, including immunomodulation, diuresis, and bactericidal activity **(Welsh et al., 2016).** Adrenomedullin possesses a very short half-life; nevertheless, it may be accurately measured by an automated assay that identifies a stable mid-regional fragment of pro-adrenomedullin (MR-pro-ADM) **(Caruhel et al., 2009).**

Increased plasma levels of mid-regional fragment of pro-adrenomedullin have been observed in numerous cardiovascular, renal, and inflammatory illnesses and are proposed to correlate with disease severity **(Potocki et al., 2009).** A prospective observational investigation demonstrated that MR-proADM is correlated with 28-day mortality in septic cases **(Marino et al., 2014).**

Aim of Study

The goal of the work was to assess the ability of neutrophil to lymphocyte and platelet ratio and plasma Adrenomedullin, at admission, for detection and mortality prediction of SA-AKI cases admitted to an ICU.

Patients and Methods

This investigation has been carried out at Cairo university hospital moderated ICU. 60 Septic AKI cases who have been admitted to intensive care unit, of Kasr AlAiny Hospital. According to the Kidney Disease Improving Global Outcomes (KDIGO) classification according to both serum creatinine (Scr) and urine output (UO) criteria will be utilized to define acute kidney injury **(KDIGO, 2012).**

Type of study:

Cross sectional analytic study

Ethical approval:

The protocol of this thesis has been approved by ethical committee of Cairo University faculty of medicine.

Cases

Inclusion criteria:

1- Cases with sepsis at admission who develop AKI according to KDIGO criteria within the first week of ICU hospitalization.

2- Age >18 years.

3- Both sexes

Exclusion criteria:

1- Cases with chronic kidney disease undergoing renal replacement therapy.

2- Cases undergoing renal replacement therapy one week before admission to the intensive care unit.

3- Cases discharged or died within two days of the intensive care unit admission.

4- Disseminated malignancy or DIC (Disseminated Intravascular Coagulopathy).

5- Case with hematological malignancies or leukemoid reaction

6- Leukopenic cases 2ry to COVID infection

Methods

All patients were subjected to:

1- Baseline characteristics including: Sex, age, height, weight, obese or not.

2- Associated comorbidities include hypertension, diabetes mellitus, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and cirrhosis.

3- Main diagnosis at admission (surgical or medical).

4- Infection source (chest, skin, cardiac, renal, abdominal, others).

5- Mechanically ventilated or not.

6- KDIGO staging for cases.

7- Laboratory data at admission:

- Complete blood picture with differential including: hemoglobin (Hb), platelets, WBCs (neutrophils, lymphocytes).
- Neutrophil to lymphocyte and platelet ratio at admission will be estimated as:
- (Neutrophil countx100) / (Lymphocyte count x Platelet count).
- Serum albumin.
- Renal functions (creatinine" baseline and admission").
- Arterial blood gases.
- Plasma Adrenomedullin level (Blood sample from a central venous or peripheral vein within twenty-four hours after the case was diagnosed with sepsis)

  Assay Principles:

  This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). ADM is introduced to the wells that have been pre-coated with ADM monoclonal antibody. Following incubation, a biotin-conjugated anti-human ADM antibody is introduced and binds to human ADM. Following incubation, unbound biotin-conjugated anti-human ADM antibody is removed throughout the washing step. Streptavidin-HRP is introduced and binds with the biotin-conjugated anti-human ADM antibody. After incubation unbound Streptavidin-HRP is washed away throughout a washing step. Substrate solution is then added and color develops in proportion to the amount of human ADM. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nanometers.

8- qSOFA score to be measured to all cases on admission:

- Altered mental status GCS<15
- Tachypnea RR>22
- Hypotension: SBP<100 mmHg

9- Length of ICU stay.

10- Follow up lab results after 48 hrs

11- Central venous O2 saturation on admission and after 48 hrs

12- Echocardiography: Echocardiography is a quick, noninvasive, thorough heart evaluation method for cases exhibiting hemodynamic instability. Echocardiography may guide fluid therapy in cases with sepsis and septic shock by assessing the collapsibility of the inferior vena cava. Sepsis-induced myocardial dysfunction may be diagnosed, and therapeutic responses may be followed using echocardiography. Cases exhibiting chronic shock must be

assessed for right heart failure or tamponade if they fail to respond to resuscitation and norepinephrine administration.

13 - Need of vasopressor, Renal Replacement Therapy and Mechanical Ventilation

14- Outcome (died-survived).

Results

Table (1): Baseline characteristics of the investigated cases

		Total no. = 60
Age (years)	Mean ± SD	58.67 ± 14.61
	Range	22 – 87
Gender	Female	18 (30.0%)
	Male	42 (70.0%)
Weight (kg)	Mean ± SD	88.83 ± 16.37
	Range	60 – 130
Height (cm)	Mean ± SD	171.90 ± 5.14
	Range	160 – 180
BMI (Kg/m^2)	Mean ± SD	30.13 ± 5.92
	Range	22 – 46.9

This table shows demographic characteristics of the included cases; 70% were male and 30% were female. The mean age was 58.67 ± 14.61 years, the mean of their weight was 88.83 ± 16.37 Kg, and the mean for their BMI was 30.13 ± 5.92 Kg/m^2.

Table (2): Diagnosis, qSOFA score, Source of sepsis and KDIGO stage at admission:

		Total no. = 60
Diagnosis at admission (med/surg)	Sepsis	27 (45.0%)
	Septic shock	33 (55.0%)
Q SOFA score	Mean ± SD	2.43 ± 0.50
	Range	2 – 3
Source of sepsis	Respiratory	25 (41.7%)
	Abdominal	12 (20.0%)
	Wound infection	3 (5.0%)
	Abscess	3 (5.0%)
	Perforated viscus	2 (3.3%)
	Line sepsis	2 (3.3%)
	Others	15 (25.0%)

KDIGO stage	1	17 (28.3%)
	2	22 (36.7%)
	3	21 (35.0%)

Most of the included cases had septic shock (55%) while about 45% had only sepsis. The mean of their SOFA score was 2.43 ± 0.50. The most common source of sepsis was respiratory (41.7%), and abdominal (20%) causes. As regards KIDGO staging of our cases most of the included cases had KIDGO stage II (36.7%) and stage III (35%), followed by stage I (28.3%). As presented in table 2.

Table (3) Need for RRT on admission and after 48 hrs, Length of ICU stay (days), Need for vasopressors on admission / after 48 hrs, mechanically ventilated on admission and after 48 hrs, Number organ dysfunction other than AKI, Outcome and 28-day mortality

		Total no. = 60
Need for RRT on admission	No	60 (100.0%)
	Yes	0 (0.0%)
Need for RRT after 48 hrs	No	49 (81.7%)
	Yes	11 (18.3%)
Length of ICU stay (days)	Median (IQR)	8 (6 – 12)
	Range	3 – 22
Need for vasopressors on admission / after 48 hrs	No	24 (40.0%)
	Yes	36 (60.0%)
Mechanically ventilated (on admission)	No	30 (50.0%)
	Yes	30 (50.0%)
Need for mechanical ventilation after 48 hrs	No	26 (43.3%)
	Yes	34 (56.7%)
Number organ dysfunction other than AKI	0	8 (13.3%)
	1	21 (35.0%)
	2	18 (30.0%)
	3	6 (10.0%)
	4	7 (11.7%)
Outcome	Survivors	38 (63.3%)
	Non survivors	22 (36.7%)
28-day mortality	No	38 (63.3%)
	Yes	22 (36.7%)

None of the included cases needed RRT at admission, while 18.3% needed RRT after 48 hours. The median length of ICU stay was 8 (6-12) days. Most of the included cases needed vasopressors (60%), and mechanical ventilation after 48 hours (56.7%). 35% of the included cases had one organ dysfunction, 30% had 2 organ

dysfunctions, and 13.3% had no organ dysfunction. Mortality among the investigated cases accounted 36.7% as presented in table 3.

Table (4): Comparison between on admission and after 48 hrs regarding laboratory data among all cases

Labs		On admission	After 48 hrs	Distinction Mean ± SD	Test value	P-value
CBC (N/LP ratio)	Median (IQR) Range	3 (2 – 13) 1 – 32	3 (1.06 – 11.5) 0.4 – 48	-0.65 ± 4.31	-0.165	0.869
Plasma Adrenomedullin (Ng/l)	Median (IQR) Range	75.15 (59.39 – 98.43) 5.4 – 340	72.6 (42.74 – 101.7) 2.44 – 418.1	2.08 ± 31.11	-1.078	0.281
Renal function (creatinine) mg/dl	Median (IQR) Range	2.03 (1.9 – 2.86) 0.98 – 5	1.3 (1 – 4) 0.56 – 16	0.74 ± 3.31	-0.718≠	0.473
Lactate (mg/dl)	Median (IQR) Range	4 (3 – 4.9) 2.5 – 8	1.07 (1 – 6.4) 0.06 – 12	-0.58 ± 3.15	-1.265≠	0.206
Central Venous oxygen Saturation (%)	Mean ± SD Range	50.39 ± 7.61 33 – 66	61.29 ± 15.46 29 – 77	10.74 ± 14.42	5.721•	<0.001

There were no statistically significant changes among septic associated AKI cases between admission and after 48 hrs echocardiography findings except for IVC being significantly lower after 48 hours with p-value <0.001.

Table (5): Comparison between on admission and after 48 hrs regarding echocardiography data among all cases

ECHO		On admission	After 48 hrs	Distinction Mean ± SD	Test value	P-value
EF (%)	Mean ± SD Range	51.72 ± 9.49 18 – 65	51.42 ± 10.05 16 – 65	-0.30 ± 2.09	-1.114•	0.270
IVC diameter (mm)	Median (IQR) Range	16 (14 – 20) 9 – 26	11 (10 – 13) 7 – 18	-5.73 ± 4.17	-6.458≠	<0.001
IVC diameter (mm)	IVC Collapsibility IVC Distensibility	38 (63.3%) 22 (36.7%)	38 (63.3%) 22 (36.7%)	–	0.000•	1.000

There were no statistically significant changes among septic associated AKI cases between admission and after 48 hrs echocardiography findings except for IVC being significantly lower after 48 hours with *P*-value <0.001.

Table (7): Comparison among survivors and non survivors regarding co-morbidities of the investigated cases

		Survivors	Non survivors	Test value	P-value
		No. = 38	No. = 22		
Diabetes Mellites	Non-diabetic	25 (65.8%)	4 (18.2%)	12.646*	<0.001
	Total diabetics	13 (34.2%)	18 (81.8%)		

The previous table shows that a statistically significant relation has been observed among diabetes and mortality among sepsis associated AKI with p-value <0.001, and other comorbidities showed statistically insignificant association with mortality with p-value >0.05.

Table (8): Comparison among survivors and non survivors regarding Diagnosis on admission (med/surg) and KDIGO stage of the investigated cases

		Survivors	Non survivors	Test value	P-value
		No. = 38	No. = 22		
Diagnosis on admission	Sepsis	23 (60.5%)	4 (18.2%)	10.094*	0.001
	Septic shock	15 (39.5%)	18 (81.8%)		
KDIGO stage	1	13 (34.2%)	4 (18.2%)	8.864*	0.012
	2	17 (44.7%)	5 (22.7%)		
	3	8 (21.1%)	13 (59.1%)		

This table showed a statistically significant distinction among survivors and non-survivors of sepsis AKI cases as regards being diagnosed as septic or sepsis shock with p-value =0.001 as most of non survivors were diagnosed to have septic shock.

There was statistically significant distinction among survivors and non-survivors of sepsis AKI cases as regards KIDGO staging for renal failure with p-value =0.012 being higher stages (II, III) more among non survivors compared to survived cases.

Table (9): Comparison among survivors and non survivors regarding CBC (N/LP ratio) on admission and after 48 hrs, Plasma Adrenomedullin on admission Ng/l and after 48 hrs, Renal function (creatinine) on admission and after 48 hrs, Need for RRT after 48 hrs, Lactate on admission and after 48 hrs, Central Venous Oxygen Saturation on admission and after 48 hrs of the investigated cases (Lab data)

		Survivors	Non survivors	Test value	P-value
		No. = 38	No. = 22		
CBC (N/LP ratio) on admission	Median (IQR)	2 (1.2 – 3)	13 (8 – 18)	-4.797	<0.001
	Range	1 – 32	2 – 31		
CBC (N/LP ratio) after 48 hrs.	Median (IQR)	1.95 (1 – 3)	11.5 (7 – 16)	-4.525	<0.001
	Range	0.4 – 41	1 – 48		
Plasma Adrenomedullin on admission Ng/l	Median (IQR)	65.73 (52.98 – 75.14)	101.55 (94.6 – 146.2)	-5.476	<0.001
	Range	5.4 – 186.14	50.28 – 340		
Plasma Adrenomedullin after 48 hrs.	Median (IQR)	55.62 (29.4 – 74.01)	108.87 (90.71 – 170.28)	-5.200	<0.001
	Range	2.44 – 185.18	16.8 – 418.1		
Renal function (creatinine) on admission	Median (IQR)	2.25 (2 – 2.9)	1.85 (1.02 – 2.15)	-3.064≠	0.002
	Range	1.2 – 5	0.98 – 4		
Renal function (creatinine) after 48 hrs.	Median (IQR)	1.02 (0.9 – 1.2)	5.5 (4 – 8)	-6.249≠	<0.001
	Range	0.56 – 5.5	2.5 – 16		
Need for RRT after 48 hrs.	No	34 (89.5%)	15 (68.2%)	4.219*	0.040
	Yes	4 (10.5%)	7 (31.8%)		
Lactate on admission	Median (IQR)	3.53 (3 – 4)	4 (3 – 5.5)	-2.366≠	0.018
	Range	2.5 – 5.1	2.9 – 8		
Lactate after 48 hrs.	Median (IQR)	1 (0.9 – 1.05)	7.7 (6 – 9)	-6.337≠	<0.001
	Range	0.06 – 1.8	1.08 – 12		
Central Venous oxygen Saturation on admission	Mean ± SD	52.74 ± 6.22	46.45 ± 8.23	3.321•	0.002
	Range	40 – 66	33 – 60		
	Mean ± SD	72.39 ± 2.03	42.10 ± 7.45	23.727•	<0.001

Central Venous oxygen Saturation after 48 hrs.	Range	69 – 77	29 – 58		

A statistically significant distinction has been observed among survivors and non-survivors of sepsis AKI cases as regards creatinine level at admission and after 48 hours among non survivors compared to survived cases with p-value =0.002, <0.001.

A statistically significant distinction has been observed among survivors and non-survivors of sepsis AKI cases as regards NLP ratio at admission and after 48 hours among non survivors compared to survived cases with p-value <0.001.

A significant distinction has been observed among survivors and non-survivors of SA-AKI cases as regards plasma adrenomedullin at admission and after 48 hours among non survivors compared to survived cases with p-value <0.001.

A statistically significant need for RRT after 48 hrs has been observed among non-survived cases with sepsis associated kidney injury compared to survived cases with p-value equals 0.040

A statistically significant distinction has been observed among survivors and non-survivors of sepsis AKI cases as regards lactate at admission and after 48 hours among non survivors compared to survived cases with p-value <0.001 and was a significant predictor of mortality with p-value equals 0.009. A statistically significant distinction has been observed among survivors and non-survivors of sepsis AKI cases as regards central venous oxygen saturation at admission and after 48 hours among non survivors compared to survived cases with p-value <0.001.

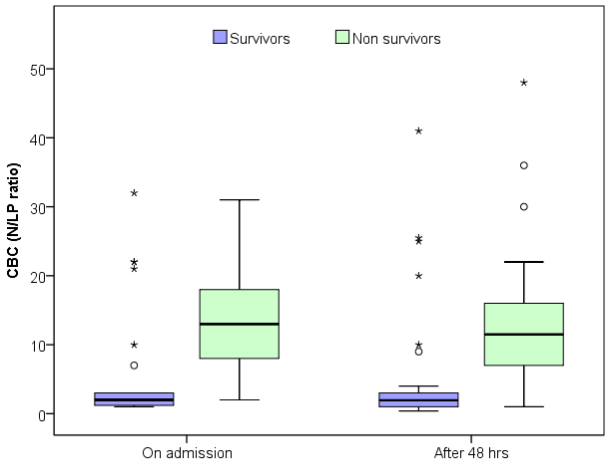


Figure (6): Comparison among survivors and non survivors regarding CBC (N/LP ratio) on admission and after 48 hrs

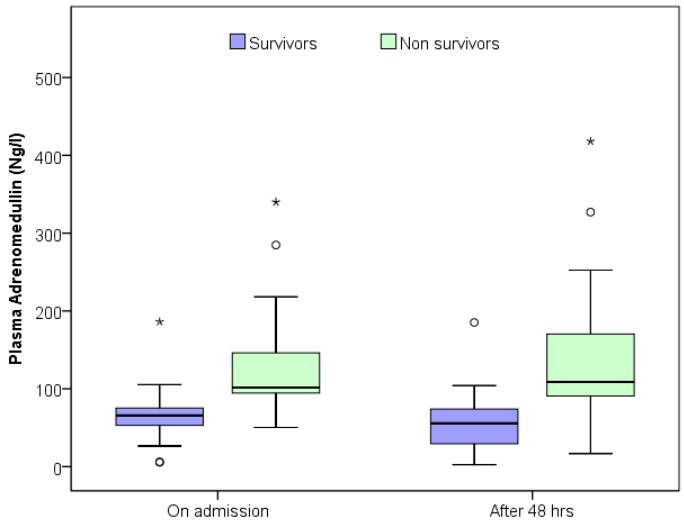


Figure (7): Comparison among survivors and non survivors regarding plasma Adrenomedullin on admission and after 48 hrs

Table (10): Comparison among survivors and non survivors regarding Echocardiography on admission and after 48 hrs of the investigated cases

		Survivors No. = 38	Non survivors No. = 22	Test value	P-value
Echocardiography on admission					
EF % on admission	Mean ± SD Range	53.82 ± 7.60 25 – 64	48.09 ± 11.39 18 – 65	2.335•	0.023
IVC diameter on admission (mm)	Median (IQR) Range	15 (14 – 18) 12 – 26	19 (12 – 22) 9 – 25	-0.978≠	0.328
IVC on admission	IVC Collapsibility IVC Distensibility	38 (100.0%) 0 (0.0%)	0 (0.0%) 22 (100.0%)	60.000*	<0.001
Echocardiography after 48 hrs					
EF % after 48 hrs	Mean ± SD Range	54.00 ± 7.54 25 – 65	46.95 ± 12.26 16 – 65	2.761•	0.008
IVC diameter after 48 hrs (mm)	Median (IQR) Range	11 (10 – 13) 7 – 18	10.5 (9 – 13) 8 – 14	-0.885≠	0.376
IVC after 48 hrs	IVC Collapsibility IVC Distensibility	38 (100.0%) 0 (0.0%)	0 (0.0%) 22 (100.0%)	60.000*	<0.001

This table showed a statistically significant lower EF, IVC collapsibility, on **admission** and after 48 hours among non-survived cases with p-value =0.023 and <0.001 correspondingly.

This table showed a statistically significant higher IVC dispensability on admission and after 48 hours among non-survived cases with p-value <0.001 correspondingly.

Table (12): Comparison among survivors and non survivors regarding length of ICU stay, need for vasopressors, mechanical ventilation (on admission and after 48 hrs) and number of organ dysfunction other than AKI

		Survivors	Non survivors	Test value	P-value
		No. = 38	No. = 22		
Length of ICU stay (days)	Median (IQR)	7 (5 – 9)	9.5 (8 – 14)	-2.928≠	0.003
	Range	3 – 20	4 – 22		
Need for vasopressors	No	22 (57.9%)	2 (9.1%)	13.828*	<0.001
	Yes	16 (42.1%)	20 (90.9%)		
Mechanically ventilated on admission	No	23 (60.5%)	7 (31.8%)	4.593*	0.032
	Yes	15 (39.5%)	15 (68.2%)		
Need for mechanical ventilation after 48 hrs	No	24 (63.2%)	2 (9.1%)	16.587*	0.000
	Yes	14 (36.8%)	20 (90.9%)		
Number organ dysfunction other than AKI	0	8 (21.1%)	0 (0.0%)	29.481*	<0.001
	1	19 (50.0%)	2 (9.1%)		
	2	10 (26.3%)	8 (36.4%)		
	3	1 (2.6%)	5 (22.7%)		
	4	0 (0.0%)	7 (31.8%)		

There was statistically significant increased length of ICU stay, need for vasopressors, need or mechanical ventilation on admission and after 48 hours and number of organ dysfunction among non survivors compared to survived SA-AKI cases with p-value =0.003, <0.001, =0.032, 0.000, and <0.001 correspondingly.

Table (13): Comparison among survivors and non survivors regarding % of change in laboratory data of the investigated cases

Labs % of change		Survivors	Non survivors	Test value	P-value
		No. = 38	No. = 22		
CBC (N/LP ratio)	Median (IQR)	0 (-47 – 28.57)	3.85 (-16.67 – 14.29)	-0.400≠	0.689
	Range	-66.67 – 100	-50 – 140		
Plasma Adrenomedullin	Median (IQR)	-5.47 (-42.9 – -0.52)	4.62 (-3.82 – 17.13)	-3.007≠	0.003

	Range	-93.2 – 28.52	-66.59 – 60.82		
Renal function (creatinin)	Median (IQR)	-53.41 (-66 – -46.27)	184.26 (121.37 – 296.04)	-6.390≠	<0.001
	Range	-77.59 – 66.67	25.63 – 1532.65		
Lactate	Median (IQR)	-73.51 (-77.5 – -65.71)	60 (25 – 118.18)	-6.345≠	<0.001
	Range	-98.5 – -60.34	-64 – 200		
Central Venous oxygen Saturation	Median (IQR)	37.25 (29.09 – 50)	-12.64 (-20 – -6)	-5.283≠	<0.001
	Range	6.06 – 82.5	-50 – 51.52		

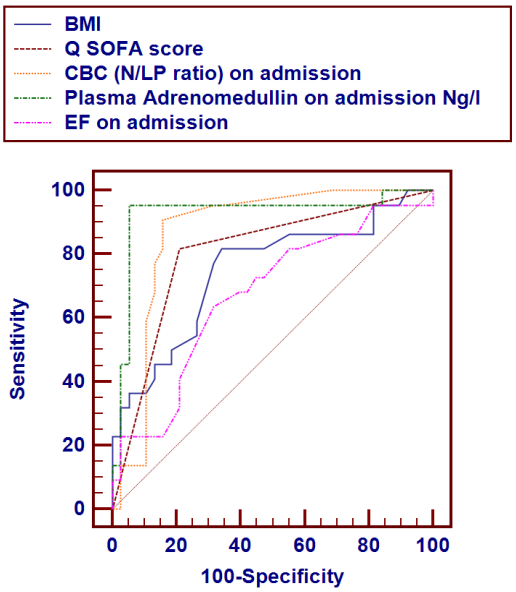
This table showed there was a statistically significant higher plasma adrenomedullin level, creatinine among non survivors while there was statistically significant lower central venous oxygen saturation among non survivors with p-value <0.001.

Table (14): Comparison among survivors and non survivors regarding % of change in ECHO data of the investigated cases

ECHO % of change		Survivors No. = 38	Non survivors No. = 22	Test value	P-value
EF%	Median (IQR)	0 (0 – 0)	0 (-5.66 – 0)	-1.990≠	0.047
	Range	-6.78 – 12.5	-16.67 – 5.45		
IVC	Median (IQR)	-28.57 (-39.13 – -22.22)	-41.29 (-50 – -12.5)	-1.642≠	0.101
	Range	-61.54 – 0	-60.87 – 33.33		

This table showed statistically significant lower EF among non survivors septic AKI cases compared to survivors with p-value =0.047.

Figure (13): ROC curve for risk factors of morality



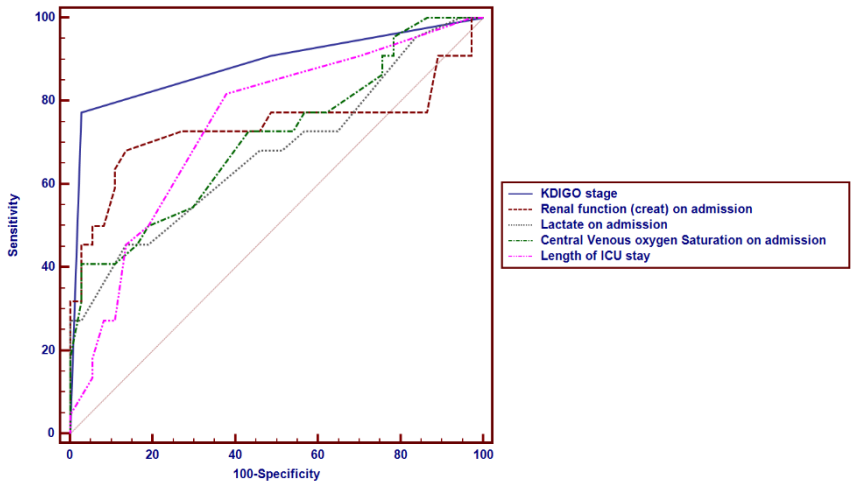


Figure (15): ROC curve for risk factors of morality

Table (15): **ROC curve for risk factors of morality:**

	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
BMI	>28.3 %	0.747	81.82	65.79	58.1	86.2

q SOFA score	>2	0.804	81.82	78.95	69.20	88.20
CBC (N/LP ratio) on admission	>3	0.871	90.91	84.21	76.9	94.1
Plasma Adrenomedullin on admission	>77.08 Ng/L	0.927	95.45	94.74	91.3	97.3
EF on admission	≤ 50 %	0.672	63.64	68.42	53.80	76.50
KDIGO stage	>2	0.886	77.27	97.37	94.40	88.10
Renal function (creat) on admission	≤ 1.99 mg/dl	0.739	68.18	86.84	75.00	82.50
Lactate on admission	>4.8 mg/dl	0.682	45.45	86.84	66.70	73.30
Central Venous oxygen Saturation on admission	≤ 42 %	0.709	40.91	97.30	90.00	73.50
Length of ICU stay	>9 days	0.727	81.82	60.53	54.50	85.20

Table (20): Univariate and Multivariate logistic regression analysis for risk factors of mortality

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper

Weight >90	**0.007**	5.333	1.594	17.846	–	–	–	–
BMI >28.3	**0.001**	8.654	2.421	30.937	–	–	–	–
Diabetes	**0.001**	8.654	2.421	30.937	**0.010**	35.292	2.341	531.983
Septic shock at admission	**0.003**	6.900	1.950	24.415	–	–	–	–
Q SOFA score >2	**0.000**	16.875	4.441	64.120	–	–	–	–
KDIGO stage	**0.014**	2.547	1.206	5.380	**0.033**	14.063	1.235	160.130
CBC (N/LP ratio) on admission >3	**0.000**	53.333	9.792	290.493	–	–	–	–
Plasma Adrenomedullin on admission Ng/l >77.08	**0.000**	378.000	32.293	4424.618	–	–	–	–
Renal function (creat) on admission ≤ 1.99	**0.000**	14.143	3.855	51.886	**0.008**	370.772	4.816	28543.541
Need for RRT after 48 hrs	**0.049**	3.967	1.007	15.618	–	–	–	–
Lactate on admission >4.8	**0.009**	5.333	1.510	18.840	–	–	–	–
Central Venous oxygen Saturation on admission ≤ 42	**0.004**	24.923	2.871	216.356	–	–	–	–
EF on admission ≤ 50	**0.018**	3.792	1.255	11.455	–	–	–	–
Mechanically ventilated on admission	**0.035**	3.286	1.085	9.952	–	–	–	–
Need for mechanical ventilation after 48 hrs	**0.000**	17.143	3.475	84.571	**0.010**	289.084	3.768	22177.590
Number organ dysfunction other than AKI	**0.000**	8.467	2.745	26.117	–	–	–	–
Length of ICU stay >9	**0.023**	3.750	1.196	11.762	–	–	–	–

The previous univariate logistic regression analysis shows that all previous variables were associated with mortality. The previous multivariate logistic regression analysis shows that there most associated factors with mortality were plasma adrenomedullin on admission >77.08, N/LP ratio on admission >3, creatinine on admission <= 1.99, presence of diabetes, requirement for mechanical ventilation upon admission and KDIGO stage.

Discussion

Sepsis is a life-threatening condition characterized by organ failure resulting from a dysregulated host response to infection **(Singer M, et al., 2016).**

Sepsis may result in numerous complications, such as sepsis-associated acute kidney injury, which frequently occurs alongside multiple organ dysfunction and leads to significantly poop clinical results **(Skube et al., 2018).**

Cases with septic acute kidney injury exhibit different characteristics compared to those with non-septic acute kidney injury, as well including higher severity scores upon admission, increased incidence of non-renal organ failure, and a greater necessity for vasopressors and mechanical ventilation. **(Bagshaw et al. 2007).**

Oxidative stress, inflammation, microvascular endothelial dysfunction, and renal tubular epithelial cell injury are the potential mechanisms underlying sepsis-associated acute kidney injury. **(Bellomo et al. 2017).**

Septic-AKI possesses different prognostic implications compared to non-septic AKI, specifically a greater short-term death rate, extended hospital stays, and an increased risk of renal function recovery upon release **(Uchino et al., 2005).** Consequently, it is essential to identify predictors of acute kidney injury and mortality to quickly avoid, diagnose, and manage these complications.

The Neutrophil to Lymphocytes and Platelets ratio has been related to acute kidney injury in emergency situations, sepsis, contrast-induced acute kidney injury, cardiovascular operation, and abdominal operation. These are readily quantifiable, efficient, and low-cost indicators of systemic inflammation that may hold potential in cases with acute kidney injury. The prognostic ability of the N/LP ratio hasn't been formerly assessed in septic acute kidney injury. **(Abu Alfeilat et al., 2017).** Adrenomedullin, a protein belonging to the calcitonin family, has been shown to significantly elevate in cases with sepsis **(Bernal Morell et al., 2018).**

The goal of this investigation was to assess the ability of neutrophil to lymphocyte and platelet ratio and plasma Adrenomedullin, at admission and after 48 hrs, for early detection and mortality prediction of septic acute kidney injury cases admitted to an intensive care unit. This investigation has been carried out on 60 cases admitted to ICU of Kasr Al-Ainy Hospital, Cairo University, diagnosed to have sepsis associated acute kidney injury; of whom 55% had septic shock and 45% had sepsis. Respiratory conditions were the main source of sepsis associated AKI (41.7%), followed by gastrointestinal causes.

In the current study, high NLP ratio > 3 on admission was a significant predictor of mortality among SA-AKI with p-value<0.001. This goes in run with Gameiro et al. study, who conducted a retrospective analysis of 399 septic-AKI cases. The Kidney Disease Improving Global Outcomes (KDIGO) classification has been utilized to define acute kidney injury. Fifty-two percent of cases have been classified as Kidney Disease Improving Global Outcomes (stage 3, 25.8 percent as Kidney Disease Improving Global Outcomes (stage 2, and 22.3 percent as Kidney Disease Improving Global Outcomes (stage 1. A greater neutrophil to

lymphocyte and platelet ratio has been identified as an independent predictor of elevated in-hospital mortality risk in septic-AKI cases, irrespective of Kidney Disease Improving Global Outcomes (stage (31.59 ± 126.8 versus 13.66 ± 22.64, P = 0.028). **Gameiro et al., 2020).**

This also is in concordance with shi., et al 2022, who conducted a retrospective study in which a total of 173 septic cases were included, 108 cases in the survival group and 65 in the death group, with a total mortality rate of 37.6%. They performed NLP ratio at day 1, 3 and 5. They found that NLP ratio was independently associated with in-hospital mortality rate (OR (odd ratio) 1.020, 95%, CI (Confidence Interval): 1.001:1.040). The AUC of NLP ratio on day one and three was 0.517 and 0.547, respectively, and the optimal cutoff value was 10.25 and 18.47. The AUC of NLP ratio on day five was 0.654, and the optimal cutoff value was 8.22. **(shi., et al 2022).**

In contrary to our study, Gameiro et al., conducted a retrospective analysis study of 450 cases who underwent major nonvascular abdominal surgery. N/LP ratio was determined in the first twelve hours following operation. AKI has been considered when developed within forty-eight hours following operation. One-hundred and one cases (22.4%) had preoperative sepsis (*p*-value less than 0.001), higher N/LP ratio (*P*-value less than 0.001) and had an increased risk of developing postoperative acute kidney injury (6.36 ± 7.34 versus 4.33 ± 3.36, (*P*-value less than 0.001). The optimal cutoff has been assessed to be more 4.86 In this cohort 29 cases died and in a multivariate analysis higher neutrophil to lymphocyte and platelet ratio wasn't associated with elevated in-hospital mortality **(Gameiro et al., 2018).**

Our thesis revealed that plasma Adrenomedullin was statistically significant predictor for mortality among SA-AKI cases with p-value<0.001. This result is consistent with Marino et al. study in which they enrolled 101 cases admitted with sepsis. Plasma samples for ADM testing have been collected upon admission and over the subsequent four days. The death rate at 28 days has been documented. ADM upon admission correlated with disease severity, as indicated by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score: P <0.001. ADM has been correlated with 28-day mortality (ADM median (IQR): survivors: 50 (31: 77) pg/mL; non-survivors: 84 (48: 232) pg/mL; P-value less than 0.001). **(Marino et al., 2014).**

However, Helmy et al. performed a study on 100 cases with proved sepsis in ICU with an age range of (53:71) years. The most frequent infection site was the respiratory tract (42%). On admission and day five readings of serum ADM, SOFA score, CRP, serum lactate level and PCT level have been estimated. Out of one hundred investigated cases, thirty-five developed septic shock. Mortality rate in the present investigation was (23%). The investigation revealed that Adrenomedullin didn't reach significant over the other variables in predicting 28-day mortality with p-value < 0.05 **(Tamer Helmy et al., 2016).**

In the current study plasma level of Adrenomedullin significantly increased with severity of illness being higher among cases with septic shock compared to cases with sepsis with *P*-value =0.017. This goes in run with Simon et al.

study which was conducted on 42 critically ill cases with sepsis and 14 cases following major surgery and found that adrenomedullin increased with severity of illness (sepsis;25.8 pg/ml, severe sepsis; 84.2 pg/ml, septic shock 119.7 pg/ml) with *P*-value =0.001 **(Simon et al., 2016).**

Similar to our outcomes, an investigation by Liu., et al was done. They included Forty-two septic cases, Adrenomedullin was collected within twenty-four hours after the case has been diagnosed with sepsis. Among the participants, sixteen cases subsequently suffered from acute kidney injury. The plasma adrenomedullin concentration in the septic acute kidney injury group was significantly elevated compared to the sepsis group without acute kidney injury (median 164.69 (118.07: 193.52) versus 76.5 (48.66: 132.31) pg/mL, P-value equals 0.0229). Adrenomedullin exhibited a sensitivity of 75 percent and a specificity of 76.92 percent at a cutoff value of 110.44 pg/mL. **(Liu., et al 2020)**

In the current study the need for RRT after 48 hours was one of significant predictors of mortality among SA-AKI with *P*-value=0.049. This goes in run with Lundberg et al. study which was conducted on 632 cases with sepsis and revealed that the need for RRT was significantly higher among non-survived cases compared to survived cases with sepsis with p-value=0.006 **(Lundberg et al., 2020).**

Our thesis results found that cases with KDIGO stage 3 AKI was associated with a higher mortality rate compared to other stage of AKI with *P*-value 0.012. This goes in run with Chang et al. study which reported that mortality rate was progressive and significant on the basis of AKI criteria more with KDIGO stage 3 AKI **(Chang et al., 2010).**

Our results showed that there was statistically significant relation between diabetes and mortality among sepsis associated acute kidney injury with *P*-value <0.001.This was in concordance with (**Hsu, Y. C. & Hsu, C. W. 2019)** who conducted a retrospective cohort investigation on a total of 696 septic cases and found that Cases with septic acute kidney injury had a higher mortality rate. The associated diabetes mellitus was correlated with septic AKI and had predictive regarding acute kidney injury and further death in septic cases.

Our results showed a statistically significant lower EF on admission and after 48 hours among non-survived cases with *P*-value =0.023 and <0.001 respectively. Our results agreement with (**Lundberg et al., 2020)** who found lower **EF** among non-survived cases than survived cases there was a statistically significant distinction among two groups with *P*-value equals 0.037

The current study revealed statistically significant longer length of hospital stay among non-survived SA-AKI cases compared to survived SA-AKI with *P*-value=0.003. This goes in run with Wang et al. study which revealed statistically significant longer length of hospital stay among non-survived SA-AKI cases compared to survived SA-AKI cases with *P*-value <0.001 **(Wang et al., 2021).** This can be explained as cases who reach maximum AKI stage by both serum creatinine and urine output criteria have the highest rates of in –hospital renal replacement therapy (RRT), longer ICU and increased mortality **(Kellum et al., 2015).**

The current study found statistically significant distinction among survivors and non-survivors of SA-AKI cases as regards being diagnosed as sepsis or septic shock with *P*-value =0.001 as most of non survivors were diagnosed to have septic shock. Our results match with Cho et al. study which was conducted on 340 SA-AKI cases to investigate the clinical characteristics of Sepsis Associated Acute Kidney Injury and revealed that non survivors had more frequently septic shock than survivors with *P*-value <0.001 **(Cho et al., 2018**).

Conclusions:

Both Adrenomedullin and NLP ratio are rapid, inexpensive and emerging biomarkers that may provide valuable insights into the pathophysiology, severity, and prognosis of sepsis-associated AKI. These biomarkers may aid in risk stratification, guiding treatment decisions, and monitoring disease progression. Plasma Adrenomedullin and NLP ratio may be reliable predictors of mortality in sepsis-associated acute kidney injury (SA-AKI) cases. Adrenomedullin and NLP ratio levels were significantly increased in SA-AKI cases, particularly in non-survivors. Adrenomedullin may play a crucial role in regulating blood pressure, vascular permeability, and immune response. The correlation between clinical manifestations and several biomarkers can enhance the diagnostic sensibility of sepsis and predict disease severity and death. Biomarkers are preferable for supporting a clinical diagnosis. We anticipate that the utilization of Adrenomedullin and NLP ratio can enhance the management and prognosis of cases with sepsis.

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