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Factors Affecting Prognosis in Sepsis Patients Admitted to Intensive Care Unit

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Abstract

In this study we aimed to examine relation between patients with prediagnosis of sepsis during ICU admission and comorbities; their vital signs, age, gender, GGT (Gamma Glutamyl Transferase), uric acid, creatinine, PLT (thrombocyte), RDW (Red Cell Distribution Width), MPV (Mean Platelet Volume), CRP (C-reactive protein) and lactate levels and whether or not these have prognostic value for mortality in sepsis.

We examined files of patients who were admitted to ICU with sepsis prediagnosis retrospectively. One hundred and fifty patients with sepsis prediagnosis were admitted to ICU between January 2014 and December 2015. Upon admission GCS (Glasgow Coma Scale), APACHE II (Acute Physiological and Chronic Health Evaluation), systolic- diastolic blood pressure (SBP-DBP) and pulse rates, uric acid, GGT, blood glucose, CRP, urea, potassium (K), sodium (Na), total cholesterol, triglyceride, WBC, lymphocyte (%), neutrophile (%), MPV, RDW, thrombocyte, arterial blood gases (ABG: Ph, PCO2, PO2, lactate, HCO3, BE) values were recorded. Also co-morbidity diseases inotropic usage were asked and recorded.

Mortality rate for 150 patients in this study was 84.7%. DBP (p=0.046), thrombocyte (p=0.008) and total cholesterol(p=0.019) levels were significantly lower and APACHE II scores (p=0.008) and creatinine (p=0.001) levels were significantly higher in deceased patients than discharged patients. There was no significant difference between groups regarding co-morbid diseases. Mortality rate was higher in patients who needed positive inotropic support during ICU admission, as expected (p=0.002)

Sepsis is a complicated, highly fatal syndrome and needs multidisciplinary approach. We concluded that APACHE II, low PLT count, low DBP, need for inotropic support, low total cholesterol levels and high creatinine levels upon ICU admission in sepsis patients can help determining prognosis. Whereas uric acid levels, RDW, MPV, WBC are not helpful.

Key words: Sepsis, İntensive Care Unit, Uric Asid, RDW, MPV

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Introduction

There are many single or multi-center epidemiological studies, studies examining factors affecting morbidity and mortality in intensive care unit patients around the world, especially regarding sepsis. Sepsis incidence is increasing worldwide. Additionally sepsis is a major cause for ICU admissions and main reason for morbidity and mortality in ICU throughout the world (1, 2). Mortality rate in patients with sepsis remains very high despite all technological improvements and intensive care and treatments (3). Mortality rates vary for systemic inflammatory response syndrome (SIRS), sepsis and septic shock but rates as high as 80 % have been reported (4, 5). Some of the reasons for high mortality rate are infectious agent that cause sepsis, age, mechanical ventilation, invasive procedures, comorbidities (respiratory, cardiovascular, renal, hematological, neurological etc.) and underlying risk factors (4, 6, 7). There are many articles about sepsis, causes of sepsis, infectious agents, mortality and diagnostic biomarkers (8, 9). Some of the biomarkers did not make to routine clinical practice because of contradictory results from studies, difficulties to adapt routine test methods or limited benefit (10,14,15). In this study we aimed to examine relation between patients with prediagnosis of sepsis during ICU admission and comorbities; their vital signs, age, gender, GGT (Gamma Glutamyl Transferase), uric acid, creatinine, PLT (thrombocyte), RDW (Red Cell Distribution Width), MPV (Mean Platelet Volume), CRP (C-reactive protein) and lactate levels and whether or not these have prognostic value for mortality in sepsis.

Material and Method

Setting

This study is conducted in Erzurum Regional Research and Training Hospital ICU. This hospital is a training hospital including all branches except obstetrics and gynecology and has 550 beds. Semi-closed ICU has 18 beds and managed by anesthesiologists 24/7. Anesthesiologists decide admission and discharge of patients. All of the data included in this study (physical examination findings, APACHE II, GCS and laboratory tests) are routinely performed by anesthesiologist during admission to ICU. Ratio of nurse to patient number is ½ during the day and 1/3 during the night shift. There are no emergency, pulmonary and neurology ICU departments in this hospital.

After obtaining Ethical Committee approval from Erzurum Regional Research and Training Hospital (Date: 03.11.2015 Decree no: 37732058-6429) we examined files of patients who were admitted to our Anesthesiology and Reanimation ICU with sepsis prediagnosis from January 2014 to December 2015. One hundred and fifty patients with sepsis prediagnosis were admitted to our 3rd degree ICU during this period. Upon admission GCS (Glasgow Coma Scale), APACHE II (Acute Physiological and Chronic Health Evaluation), intubation state, systolic-diastolic blood pressure (SBP-DBP) and pulse rates, uric acid, GGT, blood glucose, CRP, urea, potassium (K), sodium (Na), total cholesterol, triglyceride, WBC,

lymphocyte (%), neutrophile (%), MPV, RDW, PLT, arterial blood gases (ABG: Ph, PCO2, PO2, lactate, HCO3, BE) values were recorded. In addition history of DM, hypertension (HT), congestive heart failure (CHF), acute renal failure (ARF), chronic renal failure (CRF), ischemic cerebrovascular accident (CVA), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD) were asked and recorded if present. Echocardiography (ECHO) was performed after admission and ejection fraction (EF, %), presence or absence of pulmonary hypertension (PHT), atrial fibrillation (AF) and pulmonary embolism was recorded. Drug use such as insulin, diuretic, statin, ACE inhibitors and positive inotropic support during admission were recorded.

Inclusion criteria: Patients followed in ICU for at least 1 day were enrolled if data in study protocol were accessible. We compiled patients admitted to ICU with sepsis prediagnosis according to SCCM/ESICM (European Society of Intensive Care Medicine)/ACCP criteria (Table 1).

Table 1: Diagnostic criteria for sepsis (1)

Infection:

- Documented or suspected *and* some of the followingb:
- General parameters:
- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C
- Heart rate >90 bpm or >2 SD above the normal value for age
- Tachypnea: >30 bpm
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 h)
- Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes
- Inflammatory parameters:
- Leukocytosis (white blood cell count >12,000/μl)
- Leukopenia (white blood cell count <4,000/μl)
- Normal white blood cell count with >10% immature forms
- Plasma C reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value
- Hemodynamic parameters:
- Arterial hypotensionb (systolic blood pressure <90 mmHg, mean arterial pressure <70,
- or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
- Mixed venous oxygen saturation >70%b
- Cardiac index >3.5 l min−1 m−2c,d
- Organ dysfunction parameters:
- Arterial hypoxemia (PaO2/FIO2 <300)
- Acute oliguria (urine output <0.5 ml kg−1 h−1 or 45 mM/l for at least 2 h)
- Creatinine increase ≥0.5 mg/dl
- Coagulation abnormalities (international normalized ratio >1.5 or activated partial
- thromboplastin time >60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000/μl)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)
- Tissue perfusion parameters

- Hyperlactatemia (>3 mmol/l)
- Decreased capillary refill or mottling

Severe sepsis: (1)

- Severe sepsis definition = sepsis-induced tissue hypoperfusion or
- organ dysfunction (any of the following thought to be due to the
- infection)
- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output\0.5 mL kg-1 h-1 for more than 2 h despite
- adequate fluid resuscitation
- Acute lung injury with PaO2/FiO2\250 in the absence of
- pneumonia as infection source
- Acute lung injury with PaO2/FiO2\200 in the presence of
- pneumonia as infection source
- Creatinine[2.0 mg/dL (176.8 lmol/L)
- Bilirubin[2 mg/dL (34.2 lmol/L)
- Platelet count\100,000 lL
- Coagulopathy (international normalized ratio[1.5)

Exclusion criteria: Patients followed less than 24 hours and could not be diagnosed, patients with absent laboratory findings, ABG, GCS, APACHE II, medical history and ECHO results were excluded.

Biochemical tests

Blood Gases have been working within ICU with ABL800 flex device. All examinations are delivered to the laboratory within 30 minutes . Blood count was made by Abbott, Ruby-cell dyn, and CRP was made by Siemens BN II device and nephelometry. All biochemical parameters in the study were made by Abbott Architect-C 16000 device and spectrophotometric method. The normal values of all parameters are as follows: Uric acid: 2.6 – 6.0 mg/dl, Creatinine: 0.57 – 1.11 mg/dl, Urea (mg/dl), (7.0 – 20.1), GGT: 9 – 36 U/L, Na: 136 – 145 mmol/L, K: 3.5 – 5.1 mmol/L, ve Cholesterol (mg/dl), (0 – 200) WBC (10^3/uL), (3.70 – 10.1), PLT (10^3/uL), (150 – 450), MPV (fL), (6.0 – 10.0), RDW: 11.5 – 16%, NE: 40.0 – 70.0%, LY: 20.0 – 40.0%, CRP:0-5 mg/dl, Glucose: 70-105 mg/dl.

Statistics

Continuous variables are given as Mean±SD, discontinuous variables are given as persentages. Mann Whitney U test was used to test significance of two averages, Chi-square test for significance of categorical variables. Statistically significant parameters by univariate analysis (5 items) could not be tested with collective logistic regression test because of low number of discharges; instead of it each parameter was tested separately with logistic regression analysis after adjustment for gender and statistically significant parameters were shown in results. Data were entered to SPSS v.20, $p<0.05$ was considered statistical significance.

Results

Mortality rate for 150 patients in this study was 84.7%. There was no statistical difference between mortal and discharged cases regarding age and gender (Table 2,3). DBP, PLT and total cholesterol levels

were significantly lower and APACHE II scores and creatinine levels were significantly higher in deceased patients than discharged patients (Table 2). There was no significant difference between groups regarding co-morbid diseases (Table 3). Mortality rate was higher in patients who needed positive inotropic support during ICU admission, as expected (Table 3).

Table 2: Comparison of surviving and deceased sepsis patients

Parameter	Deceased (n:127)	Discharged (n:23)	P	Total
Female (%,n)	41.7, 53	52.2, 12	0.352	43.3%
Age (year)	71.8±15.5	70.4±17.6	0,568	71.55±15.76
ICU hospitalization day	4.84±5.95	3.91±7.43	0,033	4.70±6.19
GCS (1-15 score)	7.39±3.81	8.73±3.38	0.105	7.58±3.77
APACHE II	33.06±7.54	28.48±7.22	0.008	32.36±7.65
SBP (mmHg)	82.66±27.38	93.96±29.13	0.152	84.40±27.86
DBP (mmHg)	47.65±16.72	59.04±24.58	0.046	49.43±18.54
Pulse rate/min	111.58±28.68	116.00±31.60	0.890	112.25±29.92
Uric acid (mg/dL)	8.68±3.82	9.47±3.98	0.315	8.80±3.84
GGT (U/L)	79.41±77.36	87.13±120.89	0.426	80.59±85.01
Leukocyte(10^3/uL)	15.30±8.83	14.57±10.80	0.356	15.19±9.12
PLT (10^3/uL)	181.75±90.15	242.79±100.40	0.008	191.11±94.06
Neutrophile (%)	83.56±13.03	87.53±8.42	0.132	84.17±12.50
Lymphocyte (%)	9.25±8.92	8.32±6.02	0.911	9.10±8.53
MPV (fL)	8.26±2.26	7.64±2.33	0.372	8.18±2.27
RDW (%)	16.26±3.11	15.17±3.34	0.112	16.09±3.03
CRP (mg/dl)	13.82±11.70	9.05±8.54	0.077	13.09±11.38
Glucose (mg/dl)	160.01±107.64	166.96±107.27	0.633	160.01±107.64
Triglyceride (mg/dl)	128.60±81.58	145.64±109.55	0.840	130.91±85.47
Total cholesterol (mg/dl)	113.04±42.42	137.25±49.09	0.019	116.09±43.79
Creatinine(mg/dl)	2.71±2.10	1.42±0.81	0.001	2.53±1.99
Urea (mg/dl)	72.01±54.98	53.45±32.12	0.112	69.17±52.47
K (mmol/L)	4.67±1.14	4.77±1.29	0.692	4.69±1.16
Na (mmol/L)	141.23±7.89	141.57±7.65	0.960	141.28±7.83
Ph (mean value±SD)	7.26±0.18	7.33±0.15	0.173	7.27±0.18
PO_2 (mmHg)	75.90±46.97	102.24±80.41	0.103	80.08±54.18
PCO_2 (mmHg)	40.19±17.71	41.95±16.66	0.485	40.47±17.50
Lactate	4.17±3.67	3.86±3.21	0.544	4.12±3.59
Bicarbonate	17.98±6.13	21,12±8,24	0.116	18.48±6.58
Base Excess (Mean)	-7.20±7.59	-3.93±9.28	0.166	-6.68±7.94
EF% (Mean)	51.5±9.7	52.83±10.2	0.469	51.72±9.71
Inotropic use (%,n)	89.8, 114	65.2, 15	0.002	

GGT: Gamma Glutamyl Transferase, PLT: thrombocyte, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, CRP (C-reactive protein), K: Potassium, Na: Sodium, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3: Comparison of two groups according to co-morbid diseases and drug use

Parameter	Deceased (n=127)	Discharged (n=23	P
Diabetes Mellitus(%,n)	14.2, 18	13, 3	0.886
Hypertension(%,n)	20.5, 26	26.1, 6	0.545
Acute Renal Failure (%,n)	64.6, 82	60.9, 14	0.734
Chronic Renal Failure (%,n)	12.6, 16	4.3, 1	0.251
Insulin use (%,n)	7.9, 10	4.3, 1	0.551
ACE Inhibitor use (%,n)	16.5,21	21.7,5	0.544
Diuretic use (%,n)	48.8, 62	56.2, 15	0.148
Beta- blocker (%,n)	12.6,16	13.0,3	0.953
CAD (%,n)	19.7,25	21.7,5	0.821
PHT (%,n)	27.6,25	30.4,5	0.348
Malignity (%,n)	15.0,19	4.3,1	0.168
COPD (%,n)	18.1, 23	21.7, 5	0.681
Pulmonary embolism(%,n)	2.4, 3	4.3, 1	0.114
Post cpr (%,n)	20.5, 26	8.7, 2	0.182
Statin use (%,n)	10.2,13	13.0,3	0.688
Postoperative (%,n)	9.4,12	8.7,2	0.909
Acute MI- (%,n)	7.1,9	0.0,0	0.188
Pneumonia (%,n)	16.5,21	21.7,5	0.544
Acute cholecystitis (%,n)	6.3,8	4.3,1	0.717
Old age (%,n)	7.1,9	8.7,2	0.785
Pleural effusion (%,n)	3.1,4	8.7,2	0.212
Atrial fibrillation (%,n)	15.0, 19	26.1, 6	0.188
Traffic accident (%,n)	1.6,2	0.0,0	0.545

PHT: Pulmonary hipertantion, CORD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease

After adjusting for gender, univariate regression analyses showed that initial DBP (wald: 6.4, OR: 0.4 (95% CI: 0.59-3.7), p=0.011), initial platelet count (wald: 7.6, OR:1.007 (95% CI: 1.002-1.012), p=0.006), initial creatinin elevels (wald: 7.6, OR: 0.446 (95% CI: 0.251-0.791), p=0.006), initial inotrop usage (wald: 8.4, OR: 4.633 (95% CI: 1.643-13.058), p=0.004) and APACHE II score (wald: 6.6, OR: 0.923 (95% CI: 0.868-0.981), p=0.01) were independent parameters to define mortality among sepsis patients.

Discussion

There are many studies related to sepsis. However unlike other studies we examined sepsis patients with only admission data and demonstrated that uric acid, RDW and MPV do not have effects on mortality but APACHE II, PLT count, need for inotropic support, total cholesterol and creatinine levels have effect on mortality.

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection (1).

Currently sepsis is microorganisms and their toxins mixing into blood stream and general inflammation being along with host response. Sepsis is defined as presence of infection with systemic inflammatory response syndrome (SIRS) in ACCP/SCCM (American College of Chest Physicians/Society of Critical Care Medicine) consensus conference. SIRS term applies to systemic inflammatory

response triggered by some kind of infection and non-infectious conditions. There may be findings of systemic infection and it may also occur in cases of burns, pancreatitis and other diseases (1, 4, 11, 12).

SIRS, sepsis and septic shock define consecutive clinic and pathophysiologic conditions and as condition progresses morbidity and mortality rates increase. Sepsis causes imbalance of homeostasis and endothelial dysfunction; and interruption in cardiovascular system functions and intra cellular homeostasis follow these. Cellular hypoxia and apoptosis are causes of organ dysfunction and death.

Most common causes of sepsis are gram-negative and gram-positive microorganisms; in addition to these fungi, viruses and parasites can also cause sepsis (6, 13). In this study we compiled patients admitted to ICU with sepsis prediagnosis according to SCCM/ESICM (European Society of Intensive Care Medicine)/ACCP criteria (Table 1). Inflammatory response resulting from interaction between genetically predisposed host and causative microorganism causes release of biological biomarkers that can affect prognosis. Biomarkers are biological molecules whose popularity and use increases especially in elderly and patients with co-morbid diseases because clinical symptoms are not specific and diagnostic tests have limitations; they can be used for diagnosis, monitoring response to treatment and determining prognosis (9, 14). There are studies for more than 100 biomarkers in sepsis patients including acute phase proteins, cytokines/chemokines, vasodilators, biomarkers for organ dysfunctions, vascular damage biomarkers, cell surface markers, coagulation biomarkers, receptor biomarkers and lactate. Some of the more important biomarkers are endothelin-1, triggering receptor expressed on myeloid c ells (TREM)-1, natriuretic peptides, CD64, copeptin (provasopressin), neopterine, adrenomedullin (ADM), interleukin (IL)-1β and IL-6, high mobility group box-1 protein (HMGB-1), pentraxin-3, IL-10, IL-8, lipopolysaccharide binding protein (LBP), CRP, procalcitonin and lactate (9, 14, 15). Some of the biomarkers did not make to routine clinical practice because of contradictory results from studies, difficulties to adapt routine test methods or limited benefits (14). Studies showed that commonly used CRP is not an ideal marker for diagnosis of sepsis because its plasma levels do not change in sepsis and SIRS and its levels do not differ in living and deceased patients. However when used in combination with other biomarkers and clinical scoring systems like APACHE II/III, Sepsis-related Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) CRP's diagnostic value increases (16). There are recent studies about relation between mortality rates of ICU patients and RDW (17, 18). Similar to other studies Wang et al showed that RDW is an independent determinant of mortality in ICU patients (19). Also there are recent studies about relation between serum uric acid levels and mortality. Altun et al (20) performed study in 129 İCU patients, and they concluded that the MPV values of patients measured during admission to ICU do not affect on

mortality. Results showed that there is no statistically significant relation between elevated uric acid levels from first day of ICU admission and mortality and elevated uric acid levels may only be additional risk factor in sepsis (21, 22). Our results are also similar. We compiled relations between prognosis of sepsis patients in our ICU and routine laboratory tests such as CRP, RDW, MPV, lactate, creatinine, cholesterol, PLT and uric acid. Results of CRP, RDW, MPV and uric acid were not statistically significant. PLT and total cholesterol were significantly lower (p=0.008 and p=0.019 respectively) and creatinine was significantly higher (p=0.001) in deceased patients. In addition to this DBP upon admission was significantly lower in deceased patients (p=0.046). Lactic acidosis is an important parameter to determine perfusion sufficiency/insufficiency in sepsis. Because of this lactate is mainly used to determine organ dysfunction. Lactate levels ≥4mmol/L are valuable for prediction of mortality for both acute mortality and mortality during hospitalization (23). Our results were 4.17±3.67 in deceased patients and 3.86±3.21 in living patients, difference was not statistically significant. Mean ph value in all of our patients was 7.27±0.18. While metabolic acidosis was more severe in deceased patients (7.26±0.18) than in living patients (7.33±0.15) this difference was not statistically significant (Table 2).

Vasopressor support is second choice of treatment in sepsis patients after fluid replacement (3). Upon admission 89.8% of deceased patients and 65.2% of living patients had vasopressor support and this difference was statistically significant (p=0.002). Another significant marker for prognosis of sepsis is APACHE II scoring system. Nijsten et al showed APACHE II scores were lower in surviving patients than deceased patients (18.0+6.7 and 23.6+6.9 respectively). Our results were similar: 28,48±7,22 in surviving patients and 33.06±7.54 in deceased patients (p=0.008).

Limitations

This study has important limitations. Principally we relied on diagnosis that was made by anesthesiologist upon admission. We did not examined laboratory and physical examination data after admission. Moreover patients may also be deceased because of ICU related infections, VAP (ventilator associated pneumonia) or any other complication. We have not done any study on it.

There may be several rational reasons for high mortality rate in our study. First our patients were very old; second there were several co-morbid diseases such as CHF, HT, CRF, COPD, CVA and PHT; third delay in ICU admission, nearest province to our province is 180 km far and this may have contributed to any delays in admission. Fourth some of our patients were admitted after cardiopulmonary arrest and CPR; fifth secondary infections (VAP, catheter infections etc) may have been developed during ICU hospitalization.

Conclusion

In conclusion sepsis is a complicated, highly fatal syndrome and needs multidisciplinary approach. We concluded that APACHE II, PLT count, low DBP,

need for inotropic support, low total cholesterol levels and high creatinine levels upon ICU admission in sepsis patients can help determining prognosis. Whereas uric acid levels, RDW, MPV, WBC are not helpful.

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