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# Colistin-induced nephrotoxicity and risk factors in intensive care unit: estimating from the routine laboratory findings

**Ahmet Ziya Şahin[1]*, Kocamer Şimşek Betul[2]**

## Abstract

**Objective:** In this study we aimed to evaluate the patients treated with colistin in an intensive care unit (ICU) and risk factors emergence of acute renal failure (ARF) after colistine treatment.

**Materials and Methods:** Patients treated with colistine in the ICU between June 2016 and September 2018 were reviewed in this retrospective study. The 37 patients who were received colistine more than 3 days due to detection of Acinetobacter baumannii in culture of tracheal aspirate specimen were included in this study. Sociodemographic and clinical data and also biochemical parameters, glomerular filtration rates (GFR), APACHE-II, RIFLE and AKIN scores were examined. Patients were divided into two groups as ARF-developing and non-ARF-developing. Follow - up parameters were compared between these two groups.

**Results:** The patient group consisted of 26 males and 11 females. The mean age of the patients was 61.0 ± 19.33 years and %45 of the patients developed ARF. Mean APACHE-II score was 20.7±5.6. Mean age was significantly older in ARF patients. Onset day of colistine was significantly lower in patients with ARF. Significant relationships were found with the creatinine, albumin, AST, ALT and BUN parameters between ARF.

**Conclusion:** Older age and early initiation of colistin treatment in the ICU should be considered to be risky for ARF development. Before colistin treatment BUN, creatinine, CRP, albumin and AST levels should be considered to be risky for ARF development. After colistin treatment ALT, BUN, creatinine, urine output, platelet, AST, arterial blood gas base excess levels, urine pH, and protein amount in urine should be followed carefully.

**Keywords:** Colistin, nephrotoxicity, acute renal failure, risk factors

## Introduction

An acute increase in serum creatinine levels with acute decrease in glomerular filtration rate is defined as acute renal failure (ARF) (1). Determining the cause of kidney damage and early/ rapid intervention for failure is very important to prevent progression of kidney injury (2). ARF is a serious and widespread complication that is between 5 and 7 % of hospitalized patients with a mortality rate of % 50 to 70 (3). The most common causes of ARF in hospitalized patients are drugs, decreased renal perfusion, surgical and radiographic contrast agents. Among the drugs that cause ARF in hospitalized patients; aminoglycosides, nonsteroidal anti-inflammatory drugs, cyclosporine, piperacilin tazobactam, amphotericin B, angiotensin converting enzyme inhibitors, combinations of trimethoprim with sulphonamides are the most common (4). Colistin is a polypeptide antibiotic which has high activity against multiple drug-resistant gram-negative bacteria (5).

Because of the renal toxicity of colistin, clinical use in the past has been nearly abandoned and has been used only for topical applications (5, 6). However, increased multiple drug-resistant infections and carbapenem-resistant gram-negative bacteria (Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae) over the last ten years have led to an increase in the clinical use of colistin (7, 8).

Nephrotoxicity is defined as; patients develop one of the following criteria's while patients' renal function is normal (serum creatinine of 1.3 mg/dL. in women and 1.5 mg/dL in men):1. Increase in serum creatinine by ≥0.3 mg/dL within 48 h, 2. Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, 3. Urine volume <0.5 mL/kg/h for 6 h (9).

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1 Sanko University, Medicine Faculty, Dept. of Internal Medicine TR
2 Sanko University, Medicine Faculty, Dept. of Anesthesiology and Reanimation TR
*** Corresponding Author:** Ahmet Ziya Şahin **E-mail:** drahmetziya@hotmail.com **Phone:** +90 (506) 843 0814

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Acute renal failure (ARF) is defined as severe acute reduction in kidney function, with severe azotemia in biochemical findings and oliguria or anuria as clinical symptoms frequently (10). In this study we aimed to evaluate the patients treated with colistin in an intensive care unit (ICU) and risk factors emergence of ARF after colistine treatment.

## Material and Methods

Patients treated with colistine in the ICU were included in this retrospective study between June 2016 and September 2018 in Sanko University Medical Faculty Training Hospital. The approval for the study was obtained from the local Ethics Committee of Sanko University before collection of data. Written consent was not obtained because of retrospective file review design.

**Study population:** Patients who were received colistin more than 3 days (we administered colistin as 5mg/kg loading dose and after 2.5 mg/kg twice in a day) due to detection of Acinetobacter baumannii in culture of tracheal aspirate specimen, were included this study.

**Parameters:** Data of age, gender, rate of arrest, comorbid diseases, intubation situation and duration, glomerular filtration rates (GFR), APACHI-II, RIFLE and AKIN scores, onset day of colistine, positive inotrope usage, treatment response, sepsis situation, furosemide, N.-acetyl cysteine usage, hemodialysis/hemodiafiltration history (Because of the hemodynamic instability we used hemodiafiltration instead of hemodialysis for metabolic acidosis), biochemical parameters, arterial blood gas values were examined. In addition, cardiac arrest and CPR history before ICU charge, the onset day of renal dysfunction after colistine were analyzed. All these parameters and the relationship between renal dysfunction after colistine were evaluated. RIFLE criteria were used to evaluate the renal dysfunction.

**Assessment tools: RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria**: This scale is used by the clinician and assesses the renal failure injury according to the decrease in GFR rates (11). It's also used to colistine associated nephrotoxicity (12).

**APACHE (Acute Physiology, Age, Chronic Health Evaluation):** This scale is used by the clinician and assesses the severely ill hospitalized patients. This scale assess the risk estimates for hospital mortality of patients in ICU (13)

**Statistical analysis:** Descriptive statistics were used to evaluate the demographic characteristics. The Mann-Whitney U Test was used to compare numerical variables that did not have a normal distribution in two groups. The Chi-square test was used in the comparison of categorical variables. Windows version of SPSS 21.0 package software was used in the analyses. $P<0.05$ was considered significant.

## Results

One hundred-ten patients had been treated with colistin. Totally 3 patients had been survived. But 37 patients' hospital files were able to include the study. The patient group consisted of 26 males and 11 females. The mean age of the patients was 61.0 ± 19.33 years. Demographic data is shown in the table 1. Two of 37 patients had been diagnosed with acute pancreatitis, 16 of them had been diagnosed with cranial problems (intra-cranial hemorrhages, cerebral infarcts) 5 of them had been diagnosed with cardiopulmonary arrest and 14 of them had been diagnosed with pulmonary diseases (table 1). Pulmonary diseases were more related to ARF. Also ARF was found related to older ages. ARF was seen in male patients more, but it was not statistically significant (Table 2). Seventeen of 37 patients developed ARF. ARF had been developed on average 5th day (15-81 days). Mean APACHE-II score was 20.7±5.6. According to RIFFLE classification 1 patient had end stage renal disease (ESRD), 2 renal failures, 1 renal injury, 6 renal losses and 6 renal risks. All patients had been treated with mechanical ventilator (trans-tracheal intubated or tracheostomy). Mean mechanical ventilator duration under intubation/tracheostomy was 19.05± 20.99 days (Table 1).

There were no significant differences between patient with and without ARF according to gender (Table 2). Mean age was significantly older in patients with ARF then without ARF (Table 3). There were no significant differences between patient with and without ARF according to diagnosis, cardiopulmonary arrest situation, smoking, septic status, inotropic agents, furosemide, opaque substance usage, hemodialysis usage, nutrition type. Hemodiafiltration treatment ratio at first day of ICU was higher in patients with ARF than without ARF. Beginning of the day of colistine was significantly lower in patients with ARF then without ARF. (Table 2).

Relationship between continues variables and ARF had been evaluated at first day, the day before colistin onset, the day after colistin onset, 3rd and 5th days of colistin onset. The patients with ARF had significantly lower albumin and higher BUN, creatinine and CRP levels than patients without ARF at first day (Table 3). The patients with ARF had significantly lower albumin and higher AST levels at the day before colistin onset (table 4). The patients with ARF had significantly higher ALT, BUN, creatinine levels and urine output amount at the day after colistin onset, (Table 5). The patients with ARF had significantly lower albumin and higher AST, BUN, creatinine, platelets levels, and urine output amount at the 3rd day of colistin onset (table 6). The patients with ARF had significantly higher AST, ALT, and BUN, lower arterial blood gas base excess levels, creatinine, and urine pH, protein amount in urine and urine output amount at the 5th day of colistin onset (Table 7). There was no significant differences between patients with and without ARF according to levels of continue variables as total bilirubin, hemoglobin, daily fluid balance, lactate, Na, osmolality, pCO2, PO2, troponin, WBC, urine density, erythrocyte amount of urine in any days of the study. APACHE II scores were higher in ARF group but were not statistically significant. The onset day of colistin was significantly lower in ARF group (table 8, Graph1).

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**Table 1.** Demographic data and some clinical variables

| Variables | Mean ± SD | Median (Min–Max) | Variables | Grup | n ( % ) |
|---|---|---|---|---|---|
| **APACHE-II** | 21.41 ± 6.14 | 21 (10 - 39) | RIFLE | esrd | 1 ( 6.3% ) |
| **Days under intubation** | 19.05 ± 20.99 | 14 (0 - 110) | | failure | 2 ( 12.5% ) |
| **GFR** | 4769.56 ± 13587.69 | 101.5 (101.5 - 96.7) | | injury | 1 ( 6.3% ) |
| **Onset day of colistin** | 25.08 ± 21.68 | 17 (6 - 110) | | loss | 6 ( 37.5% ) |
| **Onset day of acute renal failure** | 5.24 ± 3.38 | 5 (1 - 15) | | risk | 6 ( 37.5% ) |
| | | | AKIN | 1 | 6 ( 37.5% ) |
| | | | | 2 | 2 ( 12.5% ) |
| | | | | 3 | 8 ( 50% ) |
| | | | Gender | M | 26 ( 70.3% ) |
| | | | | F | 11 ( 29.7% ) |

**Table 2.** Demographic Data And Some Clinical Variables according to AFR

| Variables | Group | AFR- | AFR+ | p* |
|---|---|---|---|---|
| **Gender** | M | 12 (46.2%) | 14 (53.8%) | 0.262 |
| | F | 8 (72.7%) | 3 (27.3%) | |
| **Diagnosis in ICU** | Gastrointestinal | 0 (0.0%) | 2 (100.0%) | 0.058* |
| | Cranial | 12 (75.0%) | 4 (25.0%) | |
| | Post-CPR | 3 (60.0%) | 2 (40.0%) | |
| | Pulmonary | 5 (35.7%) | 9 (64.3%) | |
| **Cardio-pulmonary resuscitated** | No | 15 (55.60%) | 12 (44.40%) | 0.99* |
| | Yes | 5 (50.00%) | 5 (50.00%) | |
| **Smoking** | No | 11 (64.7%) | 6 (35.3%) | 0.386 |
| | Yes | 9 (45.0%) | 11 (55.0%) | |
| **Survival** | No | 1 (50.00%) | 1 (50.00%) | 0.99* |
| | Yes | 19 (54.30%) | 16 (45.70%) | |
| **Inotropic agent usage** | No | 13 (65.0%) | 7 (35.0%) | 0.264 |
| | Yes | 7 (41.2%) | 10 (58.8%) | |
| **Hemodialysis** | No | 18 (62.1%) | 11 (37.9%) | 0.109* |
| | Yes | 2 (25.0%) | 6 (75.0%) | |
| **Hemodiafiltration** | No | 19 (63.3%) | 11 (36.7%) | **0.033*** |
| | Yes | 1 (14.3%) | 6 (85.7%) | |
| **Furosemide usage** | No | 14 (58.3%) | 10 (41.7%) | 0.716 |
| | Yes | 6 (46.2%) | 7 (53.8%) | |
| **Radiopaque usage** | No | 12 (44.4%) | 15 (55.6%) | 0.073* |
| | Yes | 8 (80.0%) | 2 (20.0%) | |
| **p Pearson Chi-Squared Test, p* Fisher Exact Test** | | | | |

**Table 3.** Demographic data and other variables

| | **Mean ± SD** | | |
|---|---|---|---|
| | Median (Min–Max) | | |
| Acute renal failure | **No (20)** | **Yes (17)** | **p** |
| **APACHE-II** | 20.7 ± 5.6 | 22.24 ± 6.81 | 0.46 |
| | 21.5 (13 - 31) | 21 (10 - 39) | |
| **Days under intubation** | 23.65 ± 26.51 | 13.65 ± 9.96 | 0.34 |
| | 16 (0 - 110) | 13 (2 - 47) | |
| **GFR** | 115.88 ± 51.16 | 102.44 ± 88.80 | 0.78 |
| | 107.35 (49.6 - 230) | 94.1 (49.2 – 43.27) | |
| **Onset day of colistin** | 29.6 ± 24.75 | 19.76 ± 16.55 | **0.05** |
| | 19 (9 - 110) | 15 (6 - 67) | |
| **Age** | 53.05 ± 20.36 | 70.35 ± 13.29 | **0.01** |
| | 49.5 (15 - 86) | 76 (47 - 86) | |

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**Table 4.** Laboratory Findings at The Arrival Of ICU

| | Mean ± SD<br>Median (Min–Max) | | p |
|---|---|---|---|
| **ARF** | **NO (20)** | **YES (17)** | |
| **Albumin** | 3.58 ± 0.76 | 2.93 ± 0.49 | **0.004** |
| | 3.45 (2.4 - 4.9) | 3 (2.1 - 4) | |
| **ALT** | 32.7 ± 35.95 | 25.71 ± 15.0 | 0.615 |
| | 18 (6 - 131) | 25 (6 - 59) | |
| **AST** | 32.8 ± 30.77 | 22.59 ± 8.59 | 0.749 |
| | 23 (11 - 139) | 19 (9 - 37) | |
| **Daily fluid balance** | 520.6 ± 581.75 | 912.69 ± 1307.28 | 0.604 |
| | 575 (-1276 - 1180) | 800 (-800 - 4440) | |
| **Base excess** | -2.61 ± 4.53 | -3.74 ± 4.81 | 0.467 |
| | -3.2 (-8.6 - 7.1) | -4 (-14.1 - 6.7) | |
| **BUN** | 19.22 ± 8.19 | 35.84 ± 21.72 | **0.002** |
| | 19.8 (7 - 39) | 28.5 (13.6 - 100) | |
| **Bilirubin** | 0.62 ± 0.33 | 0.8 ± 0.9 | 0.830 |
| | 0.6 (0.2 - 1.5) | 0.5 (0.2 - 4.1) | |
| **CRP** | 40.06 ± 47.03 | 106.8 ± 84.55 | **0.008** |
| | 19.65 (3 - 174) | 91.5 (5.7 - 280) | |
| **Hemoglobin** | 12.57 ± 3.42 | 11.97 ± 2.09 | 0.329 |
| | 12.1 (1.8 - 18.1) | 11.8 (8.1 - 16.4) | |
| **Potassium** | 4.07 ± 0.61 | 4.26 ± 0.58 | 0.342 |
| | 4.05 (2.8 - 5.3) | 4.2 (3.3 - 5.5) | |
| **Creatinine** | 0.81 ± 0.29 | 1.72 ± 1.49 | **0.016** |
| | 0.8 (0.39 - 1.5) | 1.1 (0.67 - 5.3) | |
| **Lactate** | 1.64 ± 0.87 | 2.09 ± 1.78 | 0.511 |
| | 1.55 (0.5 - 3.6) | 1.5 (1 - 8.5) | |
| **Sodium** | 140.15 ± 4.83 | 139.65 ± 3.0 | 0.712 |
| | 140 (130 - 152) | 140 (135 - 147) | |
| **Osmolality** | 299.25 ± 64.08 | 288.45 ± 16.36 | 0.963 |
| | 287.5 (267 - 567) | 281 (268 - 333) | |
| **$PCO_2$** | 43.28 ± 16.02 | 40.84 ± 15.12 | 0.670 |
| | 36.5 (26 - 81) | 37.5 (20 - 76) | |
| **Platelets** | 262036.5 ±104871.58 | 259711.76±131847.97 | 0.503 |
| | 279580 (77800 - 470000) | 236000 (81600 - 498000) | |
| **$PO_2$** | 131.94 ± 80.75 | 133.24 ± 84.72 | 0.951 |
| | 114 (57 - 384) | 104 (36.3 - 364) | |
| **Troponin** | 0.09 ± 0.13 | 0.19 ± 0.62 | 0.225 |
| | 0.02 (0 - 0.4) | 0.04 (0.01 - 2.6) | |
| **WBC** | 12796.38 ± 9237.0 | 13329.82 ± 8514.33 | 0.857 |
| | 13105 (8.1 - 34600) | 13050 (6.9 - 36120) | |
| **Urine output** | 1613.0 ± 772.91 | 1264.28 ± 546.97 | 0.127 |
| | 1400 (800 - 4250) | 1100 (400 - 2590) | |
| **Urine density** | 1017.9 ± 12.48 | 1014.18 ± 7.56 | 0.492 |
| | 1016.5 (1004 - 1055) | 1014 (1003 - 1030) | |
| **Urine erythrocyte** | 78.85 ± 119.74 | 127.41 ± 136.24 | 0.175 |
| | 0 (0 - 330) | 100 (0 - 330) | |
| **Urine pH** | 6.85 ± 1.03 | 6.47 ± 0.94 | 0.253 |
| | 7 (5 - 8.5) | 6.5 (5 - 8) | |
| **Urine protein** | 55.5 ± 125.2 | 41.53 ± 72.44 | 0.449 |
| | 0 (0 - 500) | 20 (0 - 300) | |

**ARF:** Acute renal failure, **ICU:** Intensive care unit, **ALT:** The alanine aminotransferase, **AST:** aspartate aminotransferase, **BUN:** Blood urea nitrogen, **CRP:** c - reactive protein, **WBC:** White-blood cell

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Table 5: Laboratory findings at the day before the colistin onset.

| | Mean ± SD | | p |
|---|---|---|---|
| | Median (Min–Max) | | |
| ARF | **NO (20)** | **YES (17)** | |
| **Albumin** | 2.77 ± 0.47 | 2.48 ± 0.28 | **0.017** |
| | 2.7 (1.9 - 3.8) | 2.5 (2.1 - 3.2) | |
| **ALT** | 93.85 ± 252.4 | 33.71 ± 33.75 | 0.217 |
| | 33 (8 - 1161) | 24 (4 - 132) | |
| **AST** | 87.8 ± 220.1 | 27.94 ± 26.22 | **0.022** |
| | 32 (10 - 1017) | 19 (5 - 93) | |
| **Daily fluid balance** | 1442.2 ± 1835.43 | 2138.29 ± 4255.79 | 0.726 |
| | 960 (-100 - 8500) | 1100 (-674 - 18000) | |
| **Base excess** | 0.18 ± 4.75 | -0.96 ± 4.18 | 0.352 |
| | -1.05 (-9 - 9.4) | -2.1 (-6 - 8.7) | |
| **BUN** | 26.72 ± 14.16 | 29.22 ± 14.97 | 0.522 |
| | 26.35 (8 - 55) | 27 (14 - 73) | |
| **Bilirubin** | 0.76 ± 0.47 | 0.67 ± 0.37 | 0.444 |
| | 0.7 (0.1 - 2.4) | 0.6 (0.3 - 1.4) | |
| **CRP** | 112.17 ± 52.33 | 143.55 ± 80.27 | 0.345 |
| | 111.5 (27 - 242) | 117 (50 - 354) | |
| **Hemoglobin** | 10.67 ± 2.24 | 10.26 ± 1.92 | 0.522 |
| | 10.45 (7.8 - 18.5) | 10.6 (6.7 - 15.1) | |
| **Potassium** | 3.84 ± 0.59 | 3.8 ± 0.69 | 0.833 |
| | 3.9 (2.6 - 4.6) | 3.8 (2.5 - 5.3) | |
| **Creatinine** | 0.74 ± 0.28 | 1.32 ± 1.25 | 0.155 |
| | 0.7 (0.3 - 1.26) | 0.8 (0.5 - 4.6) | |
| **Lactate** | 1.38 ± 0.64 | 1.62 ± 0.61 | 0.259 |
| | 1.3 (0.3 - 2.8) | 1.4 (0.6 - 2.7) | |
| **Sodium** | 144.05 ± 7.26 | 141.76 ± 5.78 | 0.303 |
| | 143.5 (130 - 164) | 140 (134 - 155) | |
| **Osmolality** | 288.4 ± 14.63 | 288.47 ± 15.44 | 0.927 |
| | 286 (265 - 329) | 288 (267 - 329) | |
| **$PCO_2$** | 54.69 ± 75.88 | 36.69 ± 9.67 | 0.891 |
| | 36.65 (21.9 - 371) | 36.6 (17.7 - 52.8) | |
| **pH** | 7.45 ± 0.07 | 7.43 ± 0.08 | 0.434 |
| | 7.45 (7.34 - 7.58) | 7.41 (7.28 - 7.59) | |
| **Platelets** | 300640.0 ± 157330.62 | 215835.53 ± 113103.94 | 0.073 |
| | 256700 (91500 - 704000) | 208000 (104 - 474000) | |
| **$PO_2$** | 130.71 ± 69.31 | 114.99 ± 46.51 | 0.737 |
| | 109.5 (52 - 308) | 111 (32 - 227) | |
| **Troponin** | 0.1 ± 0.24 | 0.12 ± 0.28 | 0.218 |
| | 0.02 (0 - 0.99) | 0.03 (0 - 1.14) | |
| **WBC** | 13496.69 ± 6072.19 | 12193.63 ± 12280.58 | 0.106 |
| | 13815 (13.8 - 29300) | 10900 (11.2 - 52740) | |
| **Urine output** | 2236.05 ± 765.06 | 1910.0 ± 1110.07 | 0.300 |
| | 2165 (1110 - 3971) | 1650 (0 - 4030) | |
| **Urine density** | 1018.3 ± 7.69 | 1015.06 ± 4.62 | 0.124 |
| | 1015.5 (1008 - 1037) | 1014 (1008 - 1025) | |
| **Urine erythrocyte** | 159.72 ± 143.95 | 219.76 ± 125.35 | 0.402 |
| | 100 (0 - 330) | 300 (0 - 330) | |
| **Urine pH** | 6.85 ± 0.93 | 6.26 ± 0.83 | 0.054 |
| | 7 (5 - 8) | 6.5 (5 - 8) | |
| **Urine protein** | 38.62 ± 30.15 | 57.71 ± 69.27 | 0.556 |
| | 30 (0 - 100) | 30 (0 - 300) | |

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**Table 6.** Laboratory Findings at The First Day After The Colistin Onset.

| Mean ± SD<br>Median (Min–Max) | | | |
|---|---|---|---|
| **ARF** | **NO (20)** | **YES (17)** | **p** |
| **Albumin** | 2.5 ± 0.32 | 2.29 ± 0.32 | 0.066 |
| | 2.5 (1.6 - 3.2) | 2.2 (1.8 - 2.9) | |
| **ALT** | 54.05 ± 62.79 | 25.06 ± 20.02 | **0.038** |
| | 37 (10 - 289) | 23 (2.1 - 76) | |
| **AST** | 36.45 ± 27.93 | 28.14 ± 23.44 | 0.165 |
| | 27.5 (14 - 131) | 21 (0.3 - 93) | |
| **Daily fluid balance** | 961.9 ± 981.29 | 922.29 ± 824.15 | 0.896 |
| | 820 (-1150 - 3488) | 800 (-364 - 2125) | |
| **Base excess** | -0.56 ± 5.15 | -2.51 ± 5.47 | 0.279 |
| | -2.05 (-7.9 - 12.3) | -3.5 (-12.6 - 7.6) | |
| **BUN** | 23.89 ± 11.38 | 53.41 ± 34.01 | **0.001** |
| | 24 (9 - 55.1) | 45 (19 - 124) | |
| **Bilirubine** | 1.07 ± 1.35 | 0.76 ± 0.4 | 0.939 |
| | 0.65 (0.2 - 6) | 0.6 (0.3 - 1.6) | |
| **CRP** | 128.34 ± 48.11 | 169.98 ± 115.75 | 0.314 |
| | 128.5 (11.9 - 197) | 156 (60.9 - 521) | |
| **Hemoglobin** | 10.35 ± 2.37 | 9.68 ± 1.07 | 0.410 |
| | 9.88 (7.2 - 17.6) | 9.68 (7.7 - 11.8) | |
| **Potassium** | 3.94 ± 0.51 | 4.21 ± 0.99 | 0.625 |
| | 4.05 (2.9 - 4.5) | 3.9 (3.2 - 7.5) | |
| **Creatinine** | 0.78 ± 0.48 | 1.62 ± 1.44 | **0.004** |
| | 0.65 (0.38 - 2.5) | 1.07 (0.5 - 6.1) | |
| **Lactate** | 1.44 ± 0.48 | 1.45 ± 0.6 | 0.942 |
| | 1.5 (0.7 - 2.5) | 1.5 (0.1 - 2.6) | |
| **Sodium** | 141.0 ± 6.28 | 141.47 ± 7.53 | 0.951 |
| | 140 (134 - 162) | 141 (135 - 168) | |
| **Osmolality** | 285.65 ± 14.25 | 286.88 ± 16.89 | 0.819 |
| | 283 (264 - 321) | 282 (266 - 334) | |
| **$PCO_2$** | 46.77 ± 25.31 | 45.76 ± 26.09 | 0.831 |
| | 39.5 (20.4 - 121) | 40 (25.1 - 139) | |
| **pH** | 7.44 ± 0.07 | 7.38 ± 0.1 | 0.051 |
| | 7.45 (7.27 - 7.54) | 7.38 (7.18 - 7.51) | |
| **Platelets** | 294176.22 ± 151850.66 | 192882.94 ± 69543.83 | **0.013** |
| | 300250 (224500 - 626600) | 192500 (90410-362600) | |
| **$PO_2$** | 122.33 ± 66.81 | 121.47 ± 57.07 | 0.726 |
| | 105.5 (41 - 296) | 104 (43.1 - 261) | |
| **Troponin** | 0.17 ± 0.37 | 0.17 ± 0.36 | 0.712 |
| | 0.03 (0 - 1.6) | 0.03 (0 - 1.24) | |
| **WBC** | 12437.66 ± 6929.69 | 11013.02 ± 8606.14 | 0.502 |
| | 12380 (9700 - 31000) | 10350 (7700 - 29200) | |
| **Urine output** | 2363.0 ± 755.19 | 1702.94 ± 688.96 | **0.009** |
| | 2300 (1350 - 3940) | 1750 (300 - 2860) | |
| **Urine dansity** | 1012± 2.21 | 1014.94 ± 6.14 | 0.350 |
| | 1015.5 (1011 - 1025) | 1013 (1007 - 1030) | |
| **Urine erythrocite** | 178.3 ± 129.44 | 197.41 ± 129.7 | 0.575 |
| | 150 (0 - 330) | 300 (20 - 330) | |
| **Urine pH** | 6.78 ± 0.55 | 6.49 ± 0.8 | 0.103 |
| | 7 (6 - 8) | 6 (5.5 - 8.5) | |
| **Urine protein** | 58.05 ± 37.69 | 47.12 ± 35.04 | 0.385 |
| | 45 (0 - 100) | 30 (0 - 100) | |

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**Table 7.** Laboratory Findings At The 3rd Day After The Colistin Onset.

| | Mean ± SD | | p |
|---|---|---|---|
| | Median (Min–Max) | | |
| **ARF** | NO (20) | YES (17) | |
| **Albumin** | 2.53 ± 0.3 | 2.3 ± 0.45 | **0.024** |
| | 2.5 (2 - 3.1) | 2.3 (1.7 - 3.5) | |
| **ALT** | 39.0 ± 29.66 | 23.0 ± 13.75 | 0.091 |
| | 31.5 (5 - 109) | 22 (2 - 44) | |
| **AST** | 47.85 ± 67.71 | 21.53 ± 10.98 | **0.024** |
| | 23.5 (16 - 313) | 20 (7 - 56) | |
| **Daily fluid balance** | 1038.2 ± 946.31 | 946.41 ± 1335.19 | 0.809 |
| | 765 (-80 - 3170) | 934 (-1275 - 3860) | |
| **Base excess** | -0.2 ± 3.29 | -2.76 ± 5.07 | 0.074 |
| | -0.15 (-6.3 - 6.1) | -3.1 (-11.4 - 6.8) | |
| **BUN** | 28.56 ± 21.28 | 67.19 ± 41.04 | **0.000** |
| | 22 (9 - 103.7) | 51 (20 - 139) | |
| **Bilirubin** | 1.3 ± 2.34 | 0.86 ± 0.43 | 0.507 |
| | 0.6 (0.4 - 11) | 0.8 (0.4 - 1.7) | |
| **CRP** | 137.34 ± 89.41 | 182.2 ± 103.27 | 0.170 |
| | 130.5 (28 - 378) | 164 (68.8 - 438) | |
| **Hemoglobin** | 10.04 ± 2.0 | 9.88 ± 1.01 | 0.636 |
| | 9.85 (6.9 - 16.1) | 10.1 (7.2 - 11.5) | |
| **Potassium** | 3.9 ± 0.51 | 4.11 ± 0.63 | 0.270 |
| | 3.85 (3.1 - 4.7) | 4.1 (2.7 - 5.2) | |
| **Creatinine** | 0.77 ± 0.4 | 2.36 ± 2.17 | **0.000** |
| | 0.65 (0.4 - 2.05) | 1.2 (0.67 - 7.9) | |
| **Lactate** | 1.41 ± 0.56 | 1.6 ± 0.66 | 0.363 |
| | 1.45 (0.6 - 3.1) | 1.4 (0.6 - 3) | |
| **Sodium** | 140.5 ± 6.01 | 141.47 ± 4.8 | 0.335 |
| | 139.5 (133 - 157) | 142 (135 - 150) | |
| **Osmolarity** | 281.35 ± 12.11 | 287.88 ± 14.61 | 0.206 |
| | 279.5 (261 - 307) | 283 (272 - 314) | |
| **$PCO_2$** | 43.12 ± 21.54 | 48.71 ± 39.1 | 0.670 |
| | 37.55 (24.6 - 105) | 38.3 (20.3 - 193) | |
| **pH** | 7.46 ± 0.04 | 7.39 ± 0.11 | **0.034** |
| | 7.46 (7.38 - 7.55) | 7.41 (7.13 - 7.54) | |
| **Platelets** | 273714.55 ± 157199.22 | 183129.41 ± 57896.17 | **0.025** |
| | 268350 (257 - 579800) | 191000 (72600 - 277000) | |
| **$PO_2$** | 133.0 ± 70.86 | 126.6 ± 54.62 | 0.763 |
| | 128 (32.6 - 269) | 126 (33.9 - 208) | |
| **Troponin** | 0.24 ± 0.54 | 0.21 ± 0.38 | 0.084 |
| | 0.03 (0 - 1.8) | 0.04 (0 - 1.17) | |
| **WBC** | 15220.05 ± 7574.56 | 24928.51 ± 57890.91 | 0.170 |
| | 12195 (10.9 - 34890) | 11400 (6.34 - 248000) | |
| **Urine output** | 2599.0 ± 892.81 | 1622.35 ± 1293.21 | **0.010** |
| | 2455 (1250 - 4080) | 1400 (0 - 4160) | |
| **Urine density** | 1014.7 ± 4.51 | 1014.06 ± 5.23 | 0.691 |
| | 1015 (1004 - 1021) | 1013 (1007 - 1024) | |
| **Urine erythrocyte** | 164.34 ± 138.71 | 178.59 ± 139.52 | 0.804 |
| | 100 (0 - 330) | 100 (0 - 330) | |
| **Urine pH** | 6.85 ± 0.95 | 6.29 ± 0.94 | 0.085 |
| | 6.7 (5 - 8.5) | 6 (5 - 8.5) | |
| **Urine protein** | 72.25 ± 103.94 | 85.94 ± 88.82 | 0.173 |
| | 25 (0 - 300) | 66 (0 - 300) | |

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**Table 8.** Laboratory Findings at The 5th Day After The Colistin Onset.

| | Mean ± SD<br>Median (Min–Max) | | p |
|---|---|---|---|
| **ARF** | NO (20) | YES (17) | |
| **Albumin** | 2.52 ± 0.35 | 2.27 ± 0.4 | 0.051 |
| | 2.55 (2 - 3.2) | 2.4 (1.5 - 2.9) | |
| **ALT** | 59.75 ± 48.12 | 29.65 ± 28.9 | **0.043** |
| | 44.96 (8 - 176) | 22 (2 - 118) | |
| **AST** | 65.52 ± 57.44 | 47.65 ± 83.36 | **0.026** |
| | 39.5 (19 - 212) | 24 (6 - 361) | |
| **Daily fluid balance** | 1008.93 ± 1014.52 | 1469.82 ± 1354.9 | 0.437 |
| | 870 (-680 - 3100) | 950 (135 - 5670) | |
| **Base excess** | -0.75 ± 3.46 | -4.14 ± 5.52 | **0.029** |
| | -1.55 (-4.7 - 7.7) | -4.1 (-13.1 - 8.2) | |
| **BUN** | 27.87 ± 23.36 | 77.44 ± 31.66 | **0.000** |
| | 21.5 (7.9 - 111) | 75 (42 - 151) | |
| **Bilirubine** | 1.38 ± 2.37 | 1.02 ± 0.54 | 0.306 |
| | 0.7 (0.2 - 11.09) | 0.9 (0.4 - 2.3) | |
| **CRP** | 117.8 ± 66.45 | 180.78 ± 86.98 | **0.017** |
| | 124 (16 - 264) | 171 (62.2 - 378) | |
| **Hemoglobin** | 9.78 ± 1.5 | 9.54 ± 1.07 | 0.784 |
| | 9.4 (7.42 - 14.1) | 9.6 (6.8 - 11.2) | |
| **Potassium** | 3.97 ± 0.79 | 4.19 ± 0.81 | 0.423 |
| | 4.04 (2.8 - 6.1) | 4.2 (2.8 - 5.7) | |
| **Creatinine** | 3.8 ± 12.56 | 2.91 ± 1.76 | **0.000** |
| | 0.7 (0.3 - 57) | 2.68 (1.15 - 7.6) | |
| **Lactate** | 2.05 ± 2.22 | 2.25 ± 1.05 | 0.090 |
| | 1.5 (0.7 - 11) | 2.1 (1 - 4.5) | |
| **Sodium** | 139.61 ± 5.8 | 134.18 ± 32.53 | 0.160 |
| | 139.5 (131 - 156) | 142 (13 - 156) | |
| **Osmolality** | 281.43 ± 17.34 | 275.24 ± 11.45 | 0.217 |
| | 281 (252 - 308) | 278 (247 - 293) | |
| **$PCO_2$** | 47.48 ± 29.28 | 54.06 ± 52.72 | 0.749 |
| | 37 (27.6 - 138) | 42 (20 - 252) | |
| **pH** | 7.43 ± 0.05 | 7.36 ± 0.11 | **0.013** |
| | 7.44 (7.25 - 7.49) | 7.38 (7.11 - 7.49) | |
| **Platelets** | 289215.69 ± 133575.07 | 181041.18 ± 84565.69 | **0.008** |
| | 267400 (128900 - 626000) | 174600 (65300 - 387000) | |
| **$PO_2$** | 124.95 ± 70.85 | 100.29 ± 54.3 | 0.249 |
| | 114.31 (2 - 265) | 101 (3.7 - 199) | |
| **Troponin** | 0.22 ± 0.61 | 0.21 ± 0.42 | 0.075 |
| | 0.02 (0 - 2.6) | 0.07 (0 - 1.8) | |
| **WBC** | 12999.59 ± 8039.1 | 23328.26 ± 54397.01 | 0.411 |
| | 11560 (12.8 - 30850) | 10000 (13.25 - 232000) | |
| **Urine output** | 2315.11 ± 947.3 | 1394.71 ± 1188.46 | 0.014 |
| | 2210 (900 - 3680) | 1080 (0 - 3800) | |
| **Urine erythrocyte** | 156.37 ± 131.5 | 215.35 ± 143.47 | 0.169 |
| | 100 (0 - 330) | 330 (11 - 360) | |
| **Urine pH** | 6.9 ± 0.94 | 6.21 ± 0.79 | 0.021 |
| | 7 (5 - 8.5) | 6.5 (5 - 7.5) | |
| **Urine protein** | 31.11 ± 29.28 | 159.71 ± 144.4 | **0.000** |
| | 27.5 (0 - 100) | 100 (15 - 500) | |
| **Urine density** | 1012.55 ± 5.61 | 1015.65 ± 5.11 | 0.090 |
| | 1011.5 (1003 - 1024) | 1014 (1009 - 1025) | |

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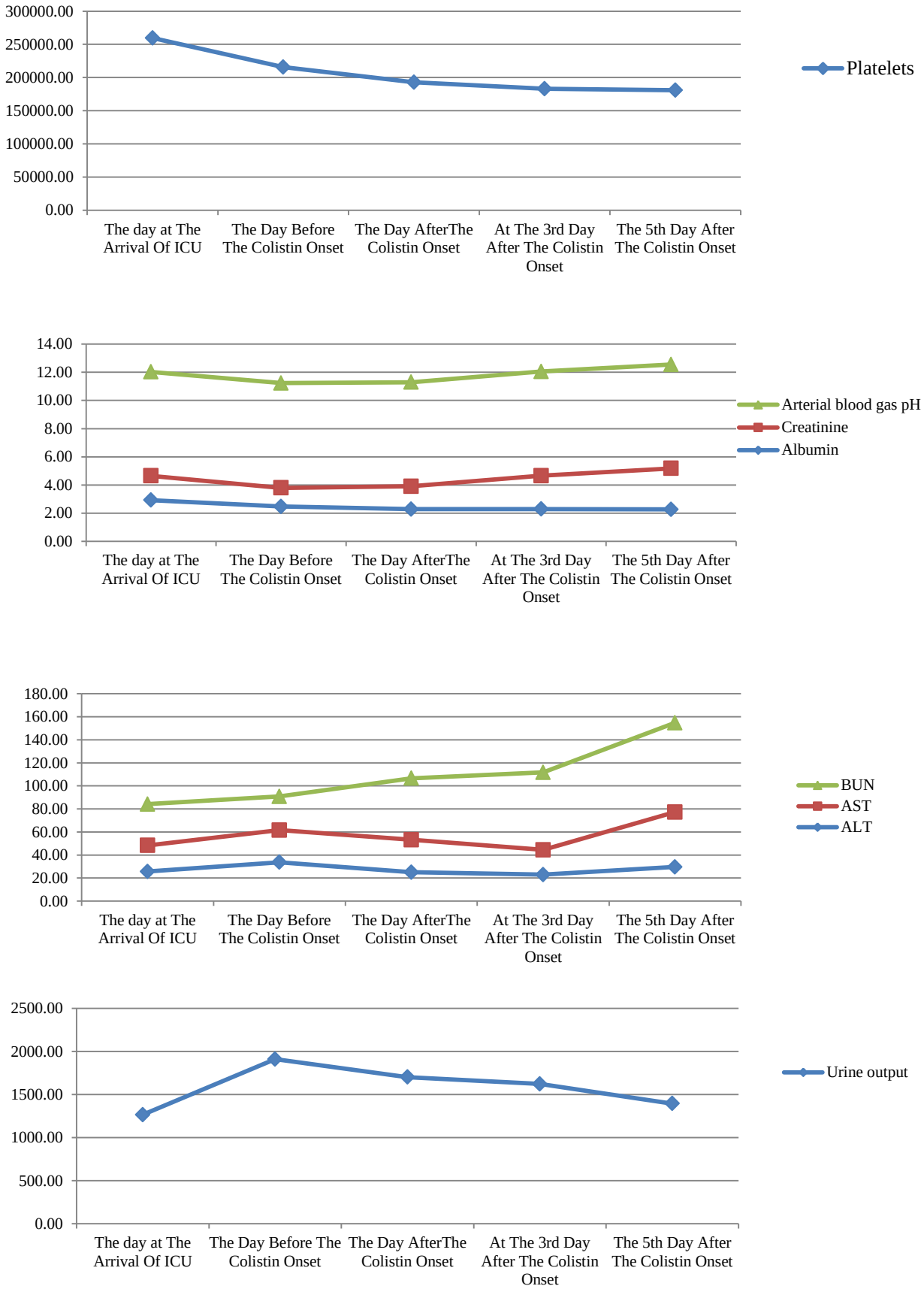


**Graph 1.** Changing blood parameters according to Colistin Onset. Graph produced from table (4-8)

## Discussion

In this study we analyzed 37 patients treated with colistin in an intensive care unit (ICU) and risk factors of ARF after colistine treatment. Seventeen of 37 patients (%45.9) had been developed ARF.

We found that patients who developed ARF were older and colistin treatments were initiated earlier than patient who did not developed ARF. Significant changes were found in the follow-up of the parameters related to ARF. In patients with ARF; BUN, creatinine and CRP levels was found to be higher while albumin lower on the first day of hospitalization before colistin. AST was found to be higher while albumin lowers the day before colistin onset. It was seen that ALT, BUN, creatinine and urine output are significantly higher just after the day of colistin treatment. On the 3rd day, the platelet height also stands out. And on the 5th day, AST, ALT, BUN, arterial blood gas base excess levels, creatinine, urine pH, protein amount in urine and urine output amount seem to be more impaired.

Comparing the groups before colistin, it may be considered that older age and early initiation of colistin treatment are risky for ARF development. Köksal et al. [14] showed that older age, presence of COPD, and DM increased the risk of nephrotoxicity. In our study, similarly older ages were related to ARF. There are several studies that revealed the association between COPD and renal failure. Mapel et al. [15] found that COPD patients have a substantially increased prevalence of renal diseases as well as abnormal renal and hepatic laboratory values. Similarly in our study, COPD was higher in ARF group but was not statistically significant.

Evaluation of nephrotoxicity by blood tests includes the measurements of blood urea nitrogen (BUN), glomerular filtration rate (GFR), concentration of serum creatinine (SCr) and creatinine clearance (CrCl). However, these assessments of nephrotoxicity are only possible when a majority of kidney function is damaged [16, 17]. Studies found that kidney injury molecule 1 (KIM-1), Cystatin C and urinary NGAL might be more reliable parameters than plasma creatinine levels to supervene renal functions during colistin medication [18,19]. But those are costly biomarkers. In this study we aimed to evaluate the routine laboratory findings can predict ARF during colistin treatment. In our study in all times most related biomarker was albumin. Similarly, previous studies showed that albumin is a good predictor for ARF (18, 20)

In a study, high APACHE II score and CRAB infection were significantly associated with 30-day mortality in ARF patients (21). But in our study APACHE II score was higher in ARF group but was not statistically significant.

Hemodiafiltration treatment ratio at first day of ICU was higher in patients with ARF. This treatment may seem more likely due to early onset of renal failure symptoms.

Clinical signs of colistin nephrotoxicity are decreased creatinine clearance and probable potential oliguria (low output of urine) or proteinuria (22). Similarly in our study, creatinine increase on the first day (end of 24 hours) of colistin treatment and additionally proteinuria on the 5th day are noteworthy in patients who developed ARF.

Studies that colistin exposure causes oxidative stress in proximal tubule cells suggest that an antioxidant strategy may be beneficial (23, 24). One of these anti-oxidant strategies is NAC usage. In a study, NAC was used at a dose of 150 mg/kg/day given to rats intraperitoneally and they reported that NAC prevented colistin-induced nephrotoxicity (25). In our study in 21 patients we used 25 mg/kg/day NAC but we did not find relationship between NAC and ARF. This can be due to low dose of NAC administration in our patients.

The retrospective design of the study and the low number of patients are limitations of this study. Patient group were not a homogenous group in terms of diagnosis. Comparisons are needed in the same diagnostic groups. Another limitation of this current study is the lack of control groups with a similar number of subjects.

## Conclusion

In this study older age and early initiation of colistin treatment in the ICU should be consider before colistine treatment for possible ARF development. Before colistin treatment BUN, creatinine, CRP, albumin and AST levels should be consider to be risky for ARF development. After colistin treatment ALT, BUN, creatinine, urine output, platelet, AST, arterial blood gas base excess levels, urine pH, protein amount in urine and urine output amount should be consider to be risky for ARF development. Also on all follow up albumin may be a good predictor for ARF. Whatever happens, Acinetobacter baumannii or colistin treatments both still have high mortality.

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