How to Cite:
Gouda, T. E. sayed, Mageed, A. A. H. A., Bahgat, M. H., & Dahab, E. A. E. A. E. (2022). Serum cystatin C and serum lactate levels as diagnostic and prognostic markers in acute kidney injury in critically ill patients. *International Journal of Health Sciences*, *6*(S4), 2594–2608.
https://doi.org/10.53730/ijhs.v6nS4.7565

Serum cystatin C and serum lactate levels as diagnostic and prognostic markers in acute kidney injury in critically ill patients

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***Abstract*---**Background: The early diagnosis of AKI in patients with sepsis would assist in more-effective care for these patients, AKI has traditionally been detected and defined by measuring surrogates of kidney-filtration function, such as plasma creatinine (pCr), urea, and, recently, plasma cystatin C (pCysC). Aim and objectives: The main aim of this study was to assess the accuracy of serum cystatin C and serum lactate as markers for diagnosis and prognosis of acute kidney injury in critically ill patients. Subjects and methods: This prospective case control study was conducted at critical care units of Specialized Medical Hospital, Mansoura University. This study was conducted on enrolled 87 critically ill-patients divided into three groups: Group A: Control (Non-AKI) group: N = 16. Group B: AKI (Recovered) group: N = 28. Group C: AKI (Non-recovered) group: N = 43. Results: It was showed a statistically significant positive correlation of low strength between serum cystatin C levels and MV duration (days), ICU-stay (days), SOFA score, serum creatinine, and serum total bilirubin, and a statistically significant negative correlation of low strength between serum cystatin C levels and both RBG and PaCO2. Conclusion: Serum

cystatin C was an effective and earlier surrogate marker of decreased renal function than SCr in ICU population. High Serum cystatin C concentrations predict substantially increased risks of short-term mortality in the ICU.

***Keywords*---**acute kidney injury, creatinine, cystatin C, lactate, prognosis, critically ill.

Introduction

In critical care, AKI remains highly prevalent, complicating the clinical course of patients, extending the need for intensive care unit (ICU) hospitalization (1). The prevalence of AKI among ICU patients varies between 30–50%, with an attributed mortality rate varying between 28–90% (2). The definition of Acute Kidney Injury (AKI) has evolved from the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria in 2004 to the Acute Kidney Injury Network (AKIN) classification in 2007(3).

AKI based on the presence of at least one of 3 following diagnostic Kidney Disease Improving Global Outcomes (KDIGO) criteria: increase in serum creatinine (SCr) by 0.3 mg/dl within 48 hours; or increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume 0.5 ml/kg/h for 6 hours (4). Serum creatinine does not accurately reflect a true glomerular filtration rate (GFR) when renal function is not in a steady state, such as during an AKI episode (5).

Kidney injury molecule-1, monocyte chemotactic peptide-1, N-acetyl-β-D-glucosaminidase, interleukin-18, liver-type fatty acid-binding protein, netrin-1, even though novel biomarkers seem to be more helpful to early detect AKI, and mortality compared to SCr, more comprehensive studies are still required to determine their clinical utility (6).

Therefore, the need for an accurate and timely biomarker to predict AKI development after renal insult is urgent. Cystatin C, a 13-kDa endogenous cysteine proteinase inhibitor, is a member of the family of proteins that has an important role in intracellular catabolism of various peptides and proteins (7) Lactate provided additional predictive value to the NEWS and NEWS plus lactate were superior to the NEWS alone in predicting unfavorable outcomes (8).

Patients presented in a state of shock, with hemodynamic instability and need for support with vasoactive amines, which in turn results in a decreased blood flow to the tissues, favouring anaerobic metabolism, with lactic acidosis and hyperlactatemia (9). High lactate levels at admission help identify patients at risk for becoming critically ill. The aim of this study was to evaluate the value of serum cystatin c and serum lactate as early and strong biomarkers fore detection of acute kidney injury and their association with adverse clinical outcomes in population of critically ill patients.

Patients and Methods

This prospective case control study was conducted on 87 critically ill patients (39 female, 48 male) above the age of 18 years old with normal SCr level, who had been admitted to medical critical care unit in Specialized Medical Hospital, Mansoura University, with different presentations and during a period of one year from February 2019 to February 2020.

Inclusion criteria: Age more than 18 years and patients with acute kidney injury diagnosed according to the recent International Kidney Disease Improving Global Outcomes (KDIGOs)

Exclusion criteria: Known history of chronic renal disease, history of nephrotoxic drugs, renal malignant patients and obstructive uropathy
All patients were reviewed for either the development of AKI or still non AKI during the period of their admission stay. Serum cystatin c and serum lactate were measured within 12 hours of admission for all patients. Baseline SCr was defined as the SCr at the time of ICU admission.

The primary end point was either the development of any stage of AKI according to KDIGO criteria and secondary endpoint was either death or improvement of the critical illness and discharge from ICU.

Patients were divided into three groups: Group A: Control (Non-AKI) group: N = 16, group B: AKI (Recovered) group: N = 28 and group C: AKI (Non-recovered) group: N = 43. The study approved by the local ethical committee of internal medicine department faculty of medicine, Mansoura University.

Ethical consideration: Study protocol will be submitted for approval by Institution Research Board (IRB) of Mansoura Medical College. Informed verbal consent will be obtained from each participant sharing in the study. Confidentiality and personal privacy will be respected in all levels of the study. Collected data will not be used for any other purpose.

All included patients were subjected to the following: The study was explained to all patients and an informed written consent was obtained from them before starting the study, if patient was unconscious, the study was explained, and informed consent was taken from first degree relative. **Careful history taking with special stress on:** Age, sex, residence, history of Diabetes Mellitus (DM) and Hypertension (HTN) and their treatment, history of Cardiac diseases and treatment, history of chronic liver disease, kidney condition (frothy urine, renal image, old SCr or any other condition related to real problems), drug history and precipitating factors of critical illness. **Clinical examination:** Thorough medical examination with special stress on: General examination: Disturbed conscious level and its degree, complexion especially cyanosis and pallor, or jaundice, edema lower limbs, vital signs (pulse, blood pressure, temperature and respiratory rate), Signs of associated co-morbidity as: (heart disease, renal disease and chronic liver disease) and signs of dehydration and possible infection **Systemic examination:** Neurological examination: Glasgow Coma Scale (GCS) was estimated, examination for motor, sensory, cerebellar, extrapyramidal

systems and pupil examination for equality and reactivity was done. Chest examination: Complete chest examination was done to detect pleurisy, pleural effusion and lung congestion. Cardiac examination: Complete cardiac examination was done to detect valvular affection, pericarditis, and pericardial effusion. Abdominal examination: Complete abdominal examination was done to detect organ size, ascites and abdominal masses.

Radiology: The kidney length was measured as the maximum longitudinal dimension (Figure 1).

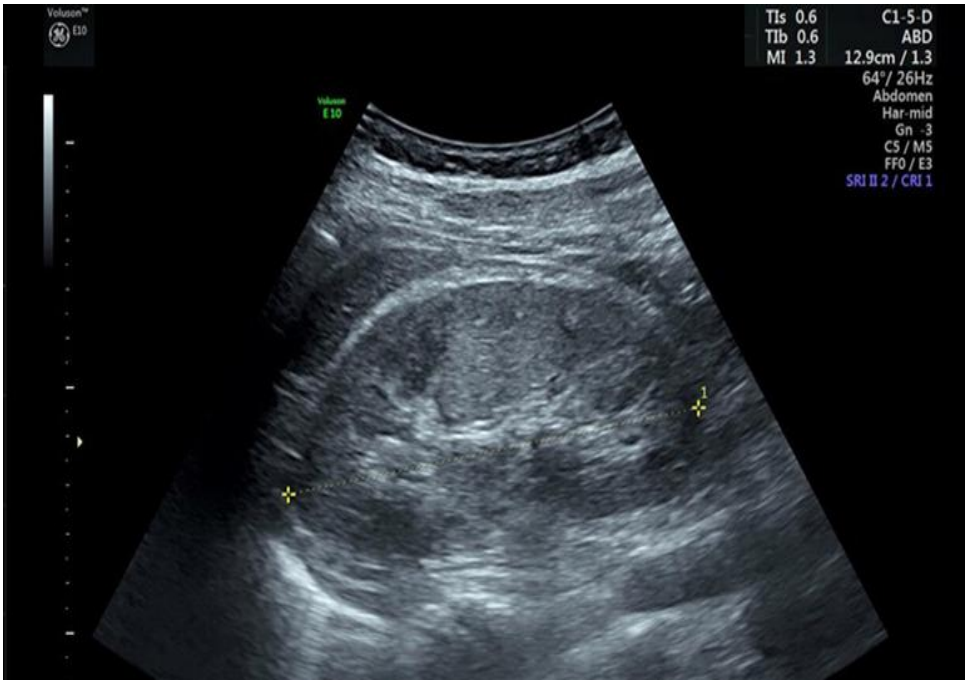

Figure 1: The kidney length was measured as the maximum longitudinal dimension

Interpretation of SOFA scores: Diagnosis of AKI: Using KDIGO Criteria for AKI diagnosing (2012) which include: increase in SCr more than 0.3 mg/dl within 48 hours and increase in SCr to more than 1.5 times of baseline SCr, which is known or presumed to have occurred within the previous 7 days.

Critically ill patients: A patient who is admitted in the regional hospital because of life threatening or potential life – threatening physiological alteration requiring intensive and vigilant medical care **(10).**

Laboratory: Blood and urine samples were withdrawn from each patient for assessment of: SCr, and repeated every 24 hours, albumin / Creatinine ratio (ACR), complete Blood Count (CBC) (WBCS, Haemoglobin, Platelet, Hematocrit), liver function test: (Serum aspartate and alanine aminotransferases (AST and ALT), serum albumin, serum bilirubin), C – Reaction protein (CRP), Erythrocyte sedimentation rate (ESR), prothrombin time and international normalized ratio (INR), serum sodium (Na) and potassium (K), ABG: Urine analysis for glucose, acetone, protein, RBCS, casts and pus, random blood sugar and GFR

Serum levels of cystatin C: Human Cystatin C ElISA KIT

Serum levels of lactate: **Diagnosis of AKI:** Using KDIGO Criteria for AKI diagnosing (2012) which include: Increase in SCr more than 0.3 mg/dl within 48 hours, increase in SCr to more than 1.5 times of baseline SCr, which is known or presumed to have occurred within the previous 7 days.
Statistical analysis: Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2019 IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results

This prospective case-control study involved 87 patients who were admitted to ICU for different indications and were followed during their ICU admission until AKI developed or not. Of these cases, 71 developed AKI comprising the **AKI group** and 16 cases did not develop AKI comprising the **non-AKI group**. The **AKI group** divided according to prognosis into 28 recovered and 43 non –recovered, Group A: Control (Non-AKI) group: N = 16, Group B: AKI (Recovered) group: N = 28 and Group C: AKI (Non-recovered) group: N = 43

There was a statistically significantly higher need for MV, HTN, and mortality and near significantly higher pneumonia and sepsis in AKI (non- recovered) vs. AKI (recovered). It also shows that one quarter of critically ill non-AKI cases died. Table (1). There was hepatic encephalopathy and DKA were higher among non-AKI and recovered AKI vs. non-recovered AKI, while ARDS and septic shock were higher among non-recovered AKI vs. non-AKI and recovered AKI. Table (2)

There was a statistically significantly higher MV duration (days), ICU-stay (days), SOFA score, and INR in non-recovered AKI vs. the two other groups. pH, $PaCO_2$ and HCO_3 were statistically significantly lower in non-recovered AKI vs. the two other groups. DBP was statistically significantly lower in non-recovered AKI vs. non-AKI. Platelet count was statistically significantly lower in non-recovered AKI and non-AKI vs. recovered AKI. Serum total bilirubin, AST, ALT and CRP were statistically significantly higher in non-recovered AKI vs. recovered AKI group. Table (3)

There was a statistically significant positive correlation of medium strength between serum lactate and serum cystatin C levels. It also shows a statistically significant positive correlation of low strength between serum cystatin C levels and MV duration (days), ICU-stay (days), SOFA score, serum creatinine, and serum total bilirubin, and a statistically significant negative correlation of low strength between serum cystatin C levels and both RBG and $PaCO_2$.near significant correlation between serum lactate and age, duration on MV and SOFA score. Table (4)

The results of binary logistic regression which was run to ascertain the effects of the listed 13 predictor variables on the likelihood that AKI patient will not recover, all were statistically significant except for sepsis. Running multivariate analysis using Enter Method revealed that only need for MV was statistically significant independent predictor of non-recovery of AKI patients. The model was statistically

significant (χ^2 [13] = 56.317, P <0.001). The model correctly classified 87.3% of cases, with 90.7% sensitivity, and 82.1specificity. Patients who required MV have 25.5-times higher odds to exhibit non-recovery. Table (5)

The test was run again using Backward Elimination Method which revealed that at step 8, 6 variables were significant independent predictors of non-recovery which are need for MV, pneumonia, SOFA score > 7, platelet count ≤ 97, AST > 96, and cystatin C > 0.1. The model was statistically significant (χ^2 [6] = 49.498, P <0.001). The model correctly classified 86% of cases, with 86% sensitivity, and 82.1specificity. Table (6)

Table (1)
Comparisons of qualitative parameters between Non-AKI groups, AKI (recovered) group and AKI (non- recovered) group

Characteristic	Control (Non-AKI) (n=16)	AKI (recovered) (n=28)	AKI (non- recovered) (n=43)	P value
Sex				0.507*
Male	9 (56.25%)	13 (46.4%)	26 (60.5%)	
Female	7 (43.75%)	15 (53.6%)	17 (39.5%)	
Shock on admission	9 (56.3%)	22 (78.6%)	32 (74.4%)	0.271
Need for mechanical ventilation	2 (12.5%) a, b	1 (3.6%) b	16 (37.2%) a	0.001
Need for dialysis	0 (0%)	1 (3.6%)	7 (16.3%)	0.114
Current smoking	4 (25%)	6 (21.4%)	12 (27.9%)	0.898
CLD	9 (56.3%)	15 (53.6%)	32 (74.4%)	0.151*
Diabetes	7 (43.8%)	19 (67.9%)	26 (60.5%)	0.296*
Hypertension	7 (43.8%) a, b	18 (64.3%) b	14 (32.6%) a	0.032*
IHD	0 (0%)	5 (17.9%)	7 (16.3%)	0.219
Stroke	2 (12.5%)	5 (17.9%)	2 (4.7%)	0.157
Upper GI bleeding	5 (31.3%)	8 (28.6%)	11 (25.6%)	0.857
Metabolic encephalopathy	3 (18.8%)	10 (35.7%)	14 (32.6%)	0.534
Dysrhythmia	7 (43.8%)	11 (39.3%)	24 (55.8%)	0.365*
Spontaneous bacterial peritonitis	1 (6.3%)	5 (17.9%)	13 (30.2%)	0.118
Pneumonia	7 (43.8%)	6 (21.4%)	20 (46.5%)	0.090*
Sepsis	5 (31.3%)	13 (46.4%)	27 (62.8%)	0.078*
Use of vasopressor drugs	6 (37.5%)	15 (53.6%)	26 (60.5%)	0.289*
Mortality	4 (25%) a	0 (0%) b	43 (100%) c	<0.001

Notes: Data are N (%). Test of significance is *Chi-Square or Fisher's exact test.

Table (2):
Comparisons of Reasons for ICU admission between Non-AKI groups, AKI (recovered) group and AKI (non- recovered) group

Cause	Control (Non-AKI) (n=16)	AKI (recovered) (n=28)	AKI (non- recovered) (n=43)
Hepatic encephalopathy (HE)	4 (25%)	8 (28.6%)	6 (14%)
DKA	3 (18%)	3 (10.7%)	1 (2.3%)
Hypovolemic shock (HVS)	4 (25%)	6 (21.4%)	3 (7%)
ARDS	2 (12.5%)	1 (3.6%)	10 (23.3%)
Aspiration pneumonia	1 (6.3%)	0 (0%)	2 (4.7%)
Septic shock (SS)	1 (6.3%)	6 (21.4%)	13 (30.2%)
Hypoglycemic coma	1 (6.3%)	0 (0%)	1 (2.3%)
Cardiogenic shock	0 (0%)	2 (7.1%)	0 (0%)
Hepatorenal syndrome	0 (0%)	1 (3.6%)	2 (4.7%)

Hypertensive encephalopathy	0 (0%)	1 (3.6%)	0 (0%)
Fulminant hepatitis	0 (0%)	0 (0%)	1 (2.3%)
Surgical cause	0 (0%)	0 (0%)	4 (9.3%)

Notes: Data are N (%)

Table (3)
Comparisons of quantitative characteristics between Non-AKI groups, AKI (recovered) group and AKI (non- recovered) group

Characteristic	Control (Non-AKI) (n=16)	AKI (recovered) (n=28)	AKI (non- recovered) (n=43)	P value
Age (years)	56 (18-89)	60 (33-80)	60 (24-85)	0.271
Duration on MV (days)	0 (0-2) a	0 (0-3) a	0 (0-5) b	0.002
ICU-Stay (days)	6 (4-8) a	7 (3-10) a	7 (4-10) b	0.001
Temperature (°C)	37 (36.2-39.1)	37 (36.2-38)	36.8 (36-38.2)	0.455
Heart rate (beat/min)	99.5 (80-140)	95 (60-140)	92 (52-130)	0.326
SBP (mmHg)	105 (80-200)	95 (50-150)	90 (70-140)	0.293
DBP (mmHg)	70 (50-100) a	60 (30-90) a, b	60 (40-90) b	0.033
Mean arterial pressure (mmHg)	81.7 (60-133.3)	71.7 (36.7-103.3)	70 (50-106.7)	0.114
Rate pressure product	10230 (6400-21800)	9000 (5050-15600)	9000 (3640-13780)	0.200
Respiratory rate (cycle/min)	24 (18-40)	21 (16-35)	20 (13-41)	0.176
NEWS SCORE	5 (2-7)	5 (2-8)	5 (2-11)	0.124
SOFA SCORE	6 (0-12) a	6 (2-11) a	8 (1-15) b	<0.001
GCS	15 (10-15)	14 (9-15)	14 (9-15)	0.363
CVP (mmHg)	13 (8-17)	13.5 (3-22)	12 (0-25)	0.997
Urine Output ml / 6-hours	700 (200-1200) a	375 (100-1000) b	300 (50-1500) b	<0.001
RBG (mg/dl)	143 (100-510)	212.5 (102-455)	153 (65-370)	0.569
Hemoglobin level (g/dl)	9.5 (5-12.4)	10.2 (7.8-13.8)	9.7 (7.3-15.8)	0.171
WBC count ($x10^3$/L)	9.3 (3.7-31) a	11.5 (2.3-28) a, b	14.4 (2.5-38.2) b	0.031
Platelet count ($x10^3$/L)	87 (37-588) a	144.5 (57-544) b	111 (19-679) a	0.026
Lymphocytic %	13.4 (10.1-19)	14.7 (8.6-22.3)	15.6 (8.2-45.7)	0.614
Serum albumin (g/dl)	2.19 (1.2-4)	2.6 (1.5-4.3)	2.2 (1.5-3.8)	0.381
Serum creatinine (mg/dl)	0.95 (0.56-1.4) a	2.15 (1.5-4.3) b	2.5 (1.6-9.8) b	<0.001
Serum total bilirubin (mg/dl)	2.27 (0.15-14.7) a, b	1.25 (0.13-14.8) a	3 (0.1-43.1) b	0.001
INR	1.44 (1.03-3) a	1.33 (1.02-2.3) a	1.6 (1-3.4) b	0.001
Ph	7.39 (7.3-7.6) a	7.4 (7.03-7.5) a	7.31 (6.93-7.50) b	<0.001
$PaCO_2$	36 (24.8-54.7) a, b	36.8 (20.2-60.1) a	32.3 (21.2-106) b	0.026
HCO_3	21.95 (17.1-31.1) a	22.7 (29.2-34.3) a	17.6 (5.8-35.3) b	<0.001
Serum sodium (mmol/l)	134 (114-146) a	131.5 (117-168) b	126 (107-153) b	0.010
Serum potassium (mmol/l)	3.4 (2.9-4.4) a	3.6 (2.5-5.3) b	4.5 (2.6-6.9) b	<0.001
CRP (mg/dl)	24 (0-26) a, b	24 (0-96) a	48 (0-96) b	0.030
AST (IU/L)	56 (9.14-471) a, b	46 (14-195) a	65 (15-1378) b	0.037
ALT (IU/L)	33.85 (8-313) a, b	31 (14-182) a	55 (13-2578) b	0.023
Serum lactate (mmol/l)	7.85 (0.2-57.6)	6.35 (1.4-15.3)	7.1 (1.6-50.5)	0.292
Cystatin C (mg/dl)	0.08 (0.001-5.2) a	0.87 (0.03-1.5) b	0.87 (0.1-7.74) b	<0.001
Estimated GFR (ml/min/1.73m²) A (MDRD creatinine formula)	79.69 ± 28.08	26.39 ± 9.01	22.51 ± 10.1	<0.001
Estimated GFR (ml/min/1.73m²) B (CKD-EPI creatinine and cystatin formula)	82.59 ± 39.74	19.41 ± 17.64	13.46 ± 8.02	<0.001

Notes: Data are median (minimum – maximum). Test of significance is Kruskal-Wallis H-test. Pairwise comparisons for significant results are presented in letters; similar letters = Insignificant difference, while different letters = Significant difference. $eGFR^A$: MDRD creatinine formula. $eGFR^B$: CKD-EPI creatinine and cystatin formula.

Table (4)
Correlation between serum lactate and cystatin C levels and study parameters (N=85)

Parameter	Serum lactate		Serum cystatin C	
	r_s	P value	r_s	P value
Serum lactate	-	-	0.336	0.001
Serum cystatin C	0.336	0.001	-	-
GCS (N=71)	-0.138	0.252	-0.076	0.531
Age (years)	0.207	0.054	0.187	0.084
Duration on MV (days)	0.190	0.079	0.232	0.031
ICU-Stay (days)	0.148	0.172	0.245	0.022
Temperature (°C)	0.091	0.403	0.067	0.538
Heart rate	-0.174	0.108	-0.055	0.612
SBP	-0.134	0.215	-0.079	0.469
DBP	-0.158	0.143	-0.172	0.111
Mean arterial pressure	-0.148	0.173	-0.118	0.275
Rate pressure product	-0.190	0.077	-0.068	0.532
Respiratory rate	-0.109	0.313	0.046	0.670
NEWS SCORE	0.036	0.743	0.058	0.431
SOFA SCORE	0.204	0.058	0.228	0.034
CVP	-0.090	0.408	-0.107	0.423
Urine Output ml / 6-hours	-0.114	0.292	-0.250	0.020
RBG (mg/dl)	-0.143	0.187	-0.212	0.049
Hemoglobin level (g/dl)	-0.091	0.399	0.073	0.503
WBC count	0.110	0.309	0.056	0.605
Platelet count	0.014	0.898	0.033	0.760
Lymphocytic %	-0.029	0.791	0.090	0.409
Serum albumin (g/dl)	-0.161	0.136	-0.037	0.736
Serum creatinine (mg/dl)	0.055	0.612	0.243	0.023
Serum total bilirubin (mg/dl)	0.110	0.310	0.220	0.041
INR	0.119	0.272	0.171	0.113
Ph	0.015	0.893	-0.102	0.345
$PaCO_2$	-0.176	0.104	-0.213	0.047
HCO_3	-0.102	0.347	-0.193	0.073
Serum sodium (mmol/l)	-0.004	0.970	-0.107	0.423
Serum potassium (mmol/l)	0.045	0.682	0.133	0.218
CRP	0.049	0.651	0.116	0.287
AST (IU/L)	0.093	0.394	0.109	0.314
ALT (IU/L)	0.101	0.350	0.103	0.345

Notes: r_s = Spearman's correlation coefficient

Table (5)
Predictors of the likelihood of non-recovery in critically ill patients with AKI (Enter Method)

Predictor variable	Univariate			Multivariate		
	P value	COR	95% CI	P value	AOR	95% CI
Need for mechanical ventilation	0.009	16	1.98-129.2	0.027	25.495	1.435 - 452.9
Pneumonia	0.036	3.2	1.1-9.4	0.055	10.580	0.954 - 117.4
Sepsis	0.177	1.9	0.74-5.1	0.156	0.1910	0.019 - 1.87
ICU-Stay (days) > 7 days	0.017	4	1.3-12.5	0.460	2.0780	0.299 - 14.43
SOFA SCORE > 7	<0.001	9.5	3.1-29.1	0.378	2.5850	0.313 - 21.36
WBC count >12.6	0.017	3.4	1.2-9.1	0.605	1.7040	0.226 - 12.86
Platelet count ≤ 97	0.011	4.4	1.4-13.6	0.095	11.491	0.655 - 201.5
Serum total bilirubin (mg/dl) > 1.7	<0.001	11.7	3.5-39.1	0.630	2.0100	0.117 - 34.5
INR > 1.4	<0.001	10.9	3.5-33.6	0.282	2.8570	0.423 - 19.3
CRP >0 (Positive)	0.005	7.4	1.8-30.2	0.188	6.0000	0.417 - 86.4
AST (IU/L) > 96	0.011	7.7	1.6-36.8	0.335	4.7390	0.200 - 112.3
ALT (IU/L) > 36	0.004	4.5	1.6-12.5	0.584	1.7080	0.252 - 11.5
Cystatin C (mg/dl) > 0.1	0.049	9.1	1.005-82.9	0.263	55.500	0.049 - 62711

Notes: COR=crude odds ratio. AOR=Adjusted odds ratio. CI=confidence interval. Test of significance is Binary logistic regression with Enter Method.

Table (6)
Predictors of the likelihood of non-recovery in critically ill patients with AKI (Backward Elimination Method)

Predictor variable	P value	AOR	95% CI
Need for mechanical ventilation	0.012	25.9	2.070 – 324.1
Pneumonia	0.021	9.7	1.404 – 67.67
SOFA SCORE > 7	0.066	4.8	0.901 – 25.99
Platelet count ≤ 97	0.003	15.8	2.525 – 98.49
AST (IU/L) > 96	0.048	12.4	1.018 – 152.1
Cystatin C (mg/dl) > 0.1	0.042	205.4	1.198 - 35222

Notes: AOR=Adjusted odds ratio. CI=confidence interval. Test of significance is Binary logistic regression with backward Elimination Method

Discussion

This was a prospective case-control conducted at critical care units of Specialized Medical Hospital, Mansoura University. All participants were subjected to careful history taking, thorough clinical examination and the laboratory and radiological data were recorded. This study was carried out on 87 enrolled critically ill-patients, who were divided into three groups: group A (non-AKI or control subjects, n=16), group B (recovered AKI patients, n=28), and group C (non-recovered AKI patients, n=43).

According to the current results, there was a statistically significant difference between the studied groups regarding need for MV that was significantly higher among non-recovered AKI group than the other two groups. In addition, hypertension and pneumonia were significantly noticed among AKI patients (both recovered and non-recovered), compared with the control non-AKI group.

Moreover, mortality, pneumonia, and sepsis were significantly reported among non-recovered AKI cases, compared with the non-AKI controls.

Sepsis-associated acute kidney injury (S-AKI) has been greatly known as a common complication in hospitalized and critically ill patients, which increases the risk of developing chronic comorbidities and is associated with extremely high mortality (11). As well, acute pneumonia, mild or severe, has been shown to cause AKI in a fraction of patients, leading to an increased in-hospital and one-year mortality (12).

In agreement with the current results is the multicenter prospective epidemiological study conducted by Wang et al. (13), who enrolled 2526 critically ill patients, and divided them into AKI group, survivors group, and non-survivors group. That study found that the need for mechanical ventilation, hypertension, chronic kidney disease, and diabetes were statistically comparable in the studied groups. Authors also found that sepsis and length of ICU stay were significantly higher in the non-survivors group. In addition, the 28-day mortality was 17.3% in whole cohort, 25.7% in AKI patients, and 10.1% in the non-AKI patients.

While, Gaygısız et al. (14) reported that sepsis incidence was significantly higher in patients with AKI, they reported that chronic cardiac disease prevalence was significantly higher in patient without AKI. In addition, chronic pulmonary disease, neurological disease, diabetes mellitus, and malignancy were comparable between AKI and non-AKI groups. Moreover, mortality was significantly higher in AKI group.

Concerning the most common reasons for ICU admission among the studied groups, the current study demonstrated that each of hepatic encephalopathy and DKA were statistically higher among the non-AKI controls and the recovered AKI cases, compared with the non-recovered AKI cases, while ARDS and septic shock were significantly higher among the non-recovered AKI cases, compared with the non-AKI controls and the recovered AKI cases.

AKI complicating ARDS portends a poor prognosis. In the ARDSnet trial, the 180-day mortality rate was much higher in those with AKI versus those without (58% vs 28%) and this association was confirmed in other prospective studies (8). Panitchote et al. (15) reported that septic shock was associated with the risk of renal non-recovery. The current literature has conflicting reports on the impact of sepsis on renal non-recovery. However, the severity and duration of AKI likely depend on the duration of the hemodynamic instability, underlying renal reserve, early treatment of sepsis, and timing of resuscitation.

In consistence with the current results, the study conducted by Wang et al. (13) demonstrated that respiratory reasons were significantly higher in non-survivors group. They also reported that post-surgery reasons were significantly higher in survivors group, when compared with non-survivors group.

While, Gaygısız et al. (14) revealed that pneumonia, COPD exacerbation, lung cancer, decompensated heart failure, sepsis, and septic shock were non-

significantly different among the studied groups. Moreover, the study found that pneumonia was the most prevalent parameter in both groups, followed by COPD exacerbation. The explanation of this difference could be related to different inclusion criteria and high mortality among AKI group in our study.

In accordance with the previous studies, Salahuddin et al. (16) reported that the most common reasons for ICU admission were severe sepsis or septic shock, followed by post-operative complications, and then respiratory failure, with statistically significant differences between patients with and without AKI. This discrepancy could be related to relatively smaller sample size in our study.

Furthermore, Tu et al., (17) who enrolled 150 septic patients were admitted in ICU. 49 patients (33%) reported at least 50% increase in SCr within 48 h of ICU admission and therefore, were diagnosed as AKI. No significant differences were noted between AKI and non-AKI groups with respect to age, gender and weight. However, ICU length of stay was longer in septic AKI group and mortality rate in septic AKI and non-AKI groups were 59% and 20%, respectively. In addition, serum total bilirubin, AST, ALT, and CRP were significantly higher in the non-recovered AKI, compared with the recovered AKI group. Also, $PaCO_2$ was significantly lower in the non-recovered AKI, compared with the recovered AKI patients.

In consistence with the current results, Wang et al. (13) reported that the SOFA score was statistically significantly higher in the non-survivors group, also the length of ICU stay was significantly longer in the non –survivors group. Also, In accordance with the previous studies, Salahuddin et al., (16) reported that in patients who developed AKI, mean arterial pressures were significantly lower with significantly higher serum lactate level. No significant differences were found in lactic acid clearance; serum lactate at 6 hour or central venous oxygen saturation (ScvO2) at admission and at 24 hour.

Salahuddin et al., (16) and Gonçalves et al., (18) also identified admission serum lactate to be independent predictor of acute kidney injury by regression analysis. Previous studies on septic patients have only investigated the impact of lactate and its change on mortality. Also, the study by Hamzić et al., (19) reported that non survivors AKI patients were statistically significantly older, with higher prevalence of septic etiology, higher Charlson Comorbidity Index (CCI) score, lower values of serum albumin, higher concentrations of CRP and ferritin as well as higher values of SCr at discharge and 3 months following discharge with lower eGRF 3 months following discharge compared to survivors.

Furthermore, Xu et al. (20) found a statistically significant higher age, SCr, APACHE II, SOFA scores, lactae, serum N-Terminal pro-brain natriuretic peptide, Charlson Comorbidity Index and need for RRT in non survivors when compared with survivors. But, there was no statistically significant difference as regard sex, presence of hypertension, ICU length stay and mechanical ventilation. Cystatin C is an endogenous biomarker of renal function produced by all nucleated cells at a near-constant rate, independent of muscle mass, and is cleared from circulation through glomerular filtration without reabsorption or secretion. CysC performs

equally as Scr as a marker of renal function in most AKI cases and outperforms Scr in some cases (21).

The current study was supported by Bongiovanni et al., (22) as they reported that in univariate analysis, CysC, sCr, and eGFR at admission were compared for the prediction of AKI development, and, moreover, their combination was evaluated. Admission CysC level > 1.44 mg/L was strongly related to the increased risk of AKI development. sCr level > 1.5 mg/dL and eGFR < 60 mL/min/1.73 m2 were also related to the increased risk of AKI, but not strongly. The best predictive model for AKI development was the combined use of CysC, sCr, and eGFR at admission; the combination of CysC + sCr had an OR = 3.48 (95% CI, 1.70–7.01, $P < 0.01$), and the combination of CysC + eGFR had an OR = 4.35 (95% CI, 1.68–8.12, $P < 0.02$).

In agreement with our result, Gaygısız et al., (14) reported that among the patients with AKI admission sCys-C levels were significantly higher when compared with non-AKI patients. Also, the study by Kwon et al., (23) reported that sCys-C was significantly correlated with mortality of critically ill AKI patients. Moreover, the current study showed that there was a statistically significant positive correlation of medium strength between serum lactate and serum cystatin C levels. It also shows a statistically significant positive correlation of low strength between serum cystatin C levels and MV duration (days), ICU-stay (days), SOFA score, serum creatinine, and serum total bilirubin, and a statistically significant negative correlation of low strength between serum cystatin C levels and both RBG and $PaCO_2$. Near significant correlation between serum lactate and age, duration on MV and SOFA score.

In agreement with the current results, Chen et al. (24) found that the highest cystatin-C (Cys-C) level was significantly associated with increased lactate levels. In similar, Uchida and Gotoh (25) revealed that the concentration of serum Cys-C was highly correlated with serum creatinine (SCr), and was mainly determined by glomerular filtration. As well, Villa et al. (26) reported that serum Cys-C is highly correlated with SCr.

In another study conducted by Fouad and Boraie (27), authors reported that Cys-C had correlated better with GFR than SCr when patients had non-severe renal dysfunction; meaning that SCr is insensitive for small decreases in GFR. On the other hand, in more severe renal impairment accompanied by a marked reduction of the GFR, Cys-C could not demonstrate any superiority over SCr.

When the test was run again using Backward Elimination method, results revealed that at step 8, 6 variables were shown to be significant independent predictors of non-recovery of AKI, which were the need for MV, pneumonia, SOFA score > 7 days, platelet count ≤ 97, AST > 96, and Cys-C > 0.1. The model correctly classified 86% of cases with 86% sensitivity, and 82.1% specificity. Similarly, Zimmerman et al. (28) reported that males, older patients, MV, and coagulopathy (prolonged PTT and PT) were significantly associated with AKI. Moreover, Benediktsson et al. (29) showed that prolonged APTT and PT at the time of ICU admission were associated with increased mortality in sepsis patients.

In accordance with the previous results, Patidar et al. (30) reported that INR, and WBC were independently associated with AKI. INR and WBC were independently associated with AKI.

Moreover, the current work found a statistically significant difference survival and non-survival patients regarding ICU stay, SOFA score, urine output, WBCs, serum creatinine, total bilirubin, INR, pH, HCO3, sodium, potassium, AST, ALT, eGFR creatinine derived, and eGFR cystatin-C derived. In conclusion, Serum cystatin-C is an effective and earlier surrogate marker of decreased renal function than SCr in ICU population. High Serum cystatin-C concentrations predict substantially increased risks of short-term mortality in the ICU. Our findings reported no significant association between serum lactate levels and AKI. We found significant correlation between serum lactate levels and Serum cystatin C.

Conclusion

Serum cystatin C was an effective and earlier surrogate marker of decreased renal function than SCr in ICU population. High Serum cystatin C concentrations predict substantially increased risks of short-term mortality in the ICU. Our findings reported no significant association between serum lactate levels and AKI. We found significant correlation between serum lactate levels and Serum cystatin C. If supported with further studies, it might be used to provide more accurate and earlier knowledge about renal dysfunction and to take appropriate preventive measures.

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