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Original article

Relation of proteinuria with severity assessment scores among intensive care unit-admitted patients at a tertiary care hospital in central India

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Abstract

Proteinuria was an indicator of both glomerular and renal endothelial injury in chronic disease, acute illness or post-surgery. Current study conducted with the aim of monitoring of proteinuria levels and predicting of mortality and morbidity of medical intensive care unit (MICU) admitted patients. Current non-randomized hospital based cross-sectional study conducted in 96 MICU admitted patients. A series of urine samples for measuring protein was taken for quantitative and qualitative measurement on day 1, day 3 and day 5. Severity of MICU admitted patients had been calculated by using APACHE II and Sequential Organ Failure Assessment (SOFA) score. Percent of patients with grade +3 proteinuria were increased from day 1 to 5. Mean APACHE II scores were significantly decreases from day 1 to 5, while mean SOFA scores was non-significantly increases from day 1 to 5. Moreover, mean values of APACHE-II (7.73 %) and SOFA (6.5 %) scores were significantly increasing with rise in levels of proteinuria on day 1, day 3 and day 5 of admission among survivors ($P < 0.05$). However, there was non-significant relationship of APACHE-II and SOFA scores with outcome by comparing values of day 1 and day 3, but proteinuria had significant relationship with outcome on day 3. Proteinuria, APACHE-II and SOFA scores at admission can be used for quantifying degree of dysfunction or failure and triage of patients into risk categories for further management. Highest APACHE-II and SOFA scores can identify critical point at which patient exhibit highest degree of organ dysfunction at MICU stay.

Keywords: Proteinuria, ICU, APACHE II score, SOFA score, Kidney injury

1. Introduction

Proteinuria was an indicator of both glomerular and renal endothelial injury in chronic disease [1], acute illness and post-surgery [2, 3]. Increased proteinuria, more specifically albumin, was related with glomerular dysfunction due to an increase in membrane permeability [4]. Glomerular proteinuria was a feature of chronic kidney disease (CKD) and intrinsic renal disease, while tubular proteinuria arises more commonly in acute kidney injury (AKI). Dipstick urinalysis was a cheap and suitable means of diagnosing proteinuria, and it was a routine test for ICU admitted patients. Proteinuria was usually observed in patients with severe burns [5].

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Acute kidney injury (AKI) was describe as a rapid loss of kidney function, which clinically manifests as an abrupt and sustained rise in urea and creatinine. Life threatening consequences of AKI includes volume overload, metabolic acidosis, hyperkalaemia and effects on other organ systems [6]. In the acute phase, as kidney function declines, AKI was related with excess mortality [7, 8], maximum Sequential Organ Failure Assessment (SOFA) and extended ICU stays [9, 10]. AKI or acute-on-chronic kidney injury (AoCKI) were commonest events among patients admitted to ICUs with incidence ranges from 20% – 50% [11]. The predominant cause of AKI or AoCKI was acute tubular necrosis (ATN). Alongside high mortality rate, ATN was related with adverse short and long term outcomes [8]. Traditional blood marker such as serum creatinine measurement had poor sensitivity and specificity because patients with AKI were not in steady state [12]. Recently, proteinuria considered as more direct biomarker of kidney injury. A large series of clinical trials had found significant correlation between the extent of proteinuria and progression to ESRD [13].

Critical care predictive scoring systems derive numerical value or severity score, from variety of measurable clinical variables and serve as helpful tool at admission in predicting the course of the patient in ICU [14]. Various severity scoring systems were SOFA (Sepsis Related Organ Failure Assessment)[15], APACHE (Acute Physiology and Chronic Health Evaluation) [16], SAPS (Simplified acute physiology score)[17], MPM-III (Mortality probability model)[18], TISS (Therapeutic intervention scoring system)[19], LODS11 (Logistic organ dysfunction score)[20], MODS (Multi organ dysfunction score) [21], GCS (Glasgow coma score), ODIN (Organ dysfunction and infection system) and TRIOS (Three-day recalibrating ICU outcomes)[22].

In majority of the scoring systems, scores were calculated from data collected on 1st day of ICU were APACHE, SAPS and MPM. Others scores were repetitive and collected on every day throughout the ICU stay or for the first 3 days such as ODIN, SOFA, MODS, LOD model and TRIOS [22]. However, SOFA, MODS and LODS were organ dysfunction scoring system. APACHE, SAPS II and MPM II were general severity scoring systems. The APACHE system was the only validated ICU risk-adjustment model that provides performance information about two separate outcomes of care (mortality and ICU length of stay) [23]. Two other validated ICU mortality prediction models, the mortality probability model III at zero hours (MPMoIII) and the simplified acute physiology score (SAPS) II, use alternative risk-adjustment methods for assessing mortality, although they had not been used for length of stay prediction [24].

APACHE score was developed in 1985 using database of North American ICU patients. The APACHE II scoring system, was simplified version of the original APACHE system and consists of three sections and widely used as ICU prognostic scoring model [25]. The SOFA score was developed in 1994 by the European Society of Intensive Care and Emergency Medicine for describing the degree of organ failure in individuals and groups of ICU patients [26]. Previous studies had shown the use of scoring systems; but currently very limited use of these scoring systems as a clinical tool for predicting the mortality even in well-established ICUs. This might be because of the lack of resources, lack of data available on the first day of admission to ICU and the time required for filling in the scoring systems. With this background, current study had been conducted with the aim of quantitative correlation between proteinuria levels and mortality risk among MICU admitted patients and comparison of Proteinuria level with APACHE-II and SOFA scores.

2. Material and Methods

Current cross-sectional study was conducted in 96 ICU admitted patients at Tertiary Care Hospital of Central India during November 2018 to October 2019 for determining the role of serial monitoring of proteinuria levels as predictor of mortality and morbidity among patients admitted in MICU (Medicine Intensive Care Unit) and comparison of proteinuria with APACHE II score and SOFA score. Before the commencement of study, ethical clearance had been obtained from Institutional ethical committee and identity of patients kept confidential. All Test cases were used in accordance with the requirements of the Rohilkhand Medical College and Hospital, Pilibhit Bypass Road, Bareilly (U.P.) Pin-243006.

Patients who were critically ill suffered from medical illnesses, which required admission to MICU and whose relative had given written informed consent were included in current study. Patients

suffering from CKD with proteinuria, Malnutrition, Protein losing enteropathy and who had not given written informed consent were excluded from study. All eligible patients based on inclusion and exclusion criteria were examined clinically and investigated for blood, urine and radiological findings performed to rule out other diseases. For proteinuria, series of urine sample was taken for quantitative and qualitative measurement of protein in urine on day 1, day 3, day 5 and before outcome of patient. Grading of proteinuria had been done by using routine Dipstick test. ICU severity of patients had been calculated by using APACHE II and SOFA scores after admission on first, third and fifth day of admission. All the patients were provided necessary treatment during ICU stay, none of the patients had been spared from necessary treatment during study period.

SOFA Scoring System: The SOFA score was simple and objective score that permits for calculation of both the number and the severity of organ dysfunction in six organ systems (respiratory, coagulation, liver, cardiovascular, renal, and neurologic) and score could measure individual or aggregate organ dysfunction [27]. SOFA scoring system analyses 6 variables such as Pao2/Fio2 ratio (for respiration), Platelets (for coagulation), Bilirubin (for liver function), Creatinine (for renal function), Glasgow coma scale (to assess level of consciousness) and Blood pressure (need for inotropic support). A score of 0 to 4 was given for each of these six variables and score obtained using sum total value of each of these parameters. The worst values on each day were recorded and organ function total score could be monitored over time [22, 26].

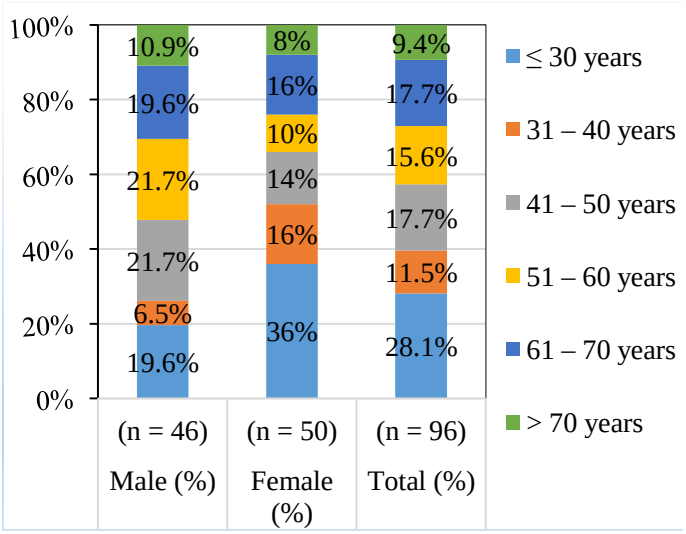
APACHE II score: It uses point scoring based on values of 12 routine physiologic measurements (taken during the first 24 hours after admission), age and previous health status for providing general measure of severity of disease. An integer scores from 0 to 71 was then calculated based on these measurements; higher scores suggests severe disease and high risk of death [28]. The 12 Physiological Variables were Temperature (Rectal or core temperature in degrees Celsius), Mean Arterial Pressure (By using formula to calculate MAP: SBP +[DBP×2]÷3), Heart Rate, Respiratory Rate, Oxygenation, Arterial pH, Serum Sodium (mmol/L), Serum Potassium (mmol/L), Serum Creatinine (mg/100mL or µmol/L), Hematocrit (%), White Blood Cell Count (total mm3 in 1000s) and Glasgow Coma Scale [22, 26].

After completion of data collection, all the data were entered in MS Excel spreadsheet and analyzes with the help of software IBM SPSS version 20.0. Qualitative data explained with frequency, percentage, and Pearson's Chi square test used for checking association, while Quantitative data explained with mean and SD and independent sample test and ANOVA test applied for checking association. P value less than 0.05 consider as statistically significant.

3.Results

During 1 year of study period, total 96 critically ill MICU admitted patients who were satisfying inclusion and exclusion criteria were enrolled in study. Mean age of the patients was 47.1 ± 19.2 years (range 15 – 92 years) and majority of the patients were ≤ 30 years old (28.1%) and females (52.1%) (Figure 1). Commonest co-morbidities among patients were diabetes (20.8%), hypertension (15.6%) and cerebrovascular accident (10.4%). Among all total 15.6% patients (n=15) were expired (Non-survivor) on or before 5th day of MICU admission.

Figure 1: Age and gender wise distribution of all patients



Urine protein levels, APACHE-II score and SOFA score were evaluated on admission, third and fifth days of MICU admission. On or before 5th day of admission, 15 patients were expired so that were not considered for Proteinuria and severity scores. Percent of patients with grade +3 proteinuria were increased

from 1st day to 5th days (2.1% vs 11.1%), however, in other categories of proteinuria, percent of patients were decreased from 1st day to 5th day (Table 1).

By applying paired sample test, mean values of APACHE II scores was non-significantly decreases from 1st day to 3rd day ($p>0.05$), but decreases significantly from 3rd day to 5th day and from 1st day to 5th day ($p<0.05$). Contrasting to this, mean values of SOFA scores was significantly increases from 1st day to 3rd day ($p<0.05$) but decreases non-significantly from 3rd day to 5th day ($p>0.05$). However, mean SOFA scores was non-significantly higher on 5th days compared to 1st day level ($p>0.05$; Table 1). By Applying One-way ANOVA test, mean values of both APACHE-II and SOFA scores were significantly increasing with increasing grades of proteinuria on 1st day, 3rd day and 5th day of admission ($p<0.05$) (Table 2).

After 5 days of admission, 84.4% patients were survivor (n=81) and 15.6% patients were non-survivor (n=15). By Applying Pearson's chi square test, there was statistically non-significant relationship of Proteinuria with outcome on 1st day ($p>0.05$), but proteinuria had statistically significant relationship with outcome on 3rd day of admission ($p<0.05$). By applying independent sample test, mean values of APACHE II scores was non-significantly lower among 5-day survivor patients compared non-survivor patients on 1st day and 3rd day of admission ($p>0.05$).

Table 1: Proteinuria, APACHE II & SOFA scores based on admission day 1, day 3 & day 5

Variables \ Day		Admission Day 1	Admission Day 3	Admission Day 5
		n = 96 (%)	n = 96 (%)	n = 81 (%)
Proteinuria	Nil	38 (39.6%)	38 (39.6%)	37 (45.7%)
	Trace	14 (14.6%)	8 (8.3%)	10 (12.3%)
	+1	26 (27.1%)	18 (18.8%)	10 (12.3%)
	+2	16 (16.7%)	29 (30.2%)	15 (18.5%)
	+3	2 (2.1%)	3 (3.1%)	9 (11.1%)
APACHE II score	Mean ± SD	20.66 ± 8.13	20.36 ± 8.83	17.99 ± 10.19
SOFA score	Mean ± SD	7.54 ± 2.68	8.13 ± 2.9	7.62 ± 3.83

Though mean values of SOFA scores were non-significantly higher on 1st day and non-significantly lower on 3rd day of admission among 5-day survivor compared to non-survivor patients ($p>0.05$; Table 3).

Table 2: Comparison of APACHE II & SOFA scores based on Proteinuria levels

Proteinuria	APACHE II score (Mean ± SD)			SOFA score (Mean ± SD)		
	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5
Nil	18.4 ± 8.0	14.5 ± 7.2	11.5 ± 8.0	6.8 ± 2.4	6.8 ± 2.8	5.9 ± 2.8
Trace	19.1 ± 8.3	19.4 ± 7.5	18.6 ± 10.1	7.2 ± 2.9	8.0 ± 2.9	7.2 ± 3.9
+1	21.3 ± 7.9	23.4 ± 7.5	21.7 ± 6.6	8.1 ± 2.7	7.7 ± 1.6	7.8 ± 3.2
+2	25.6 ± 7.2	25.4 ± 7.1	26.6 ± 7.8	8.2 ± 2.6	9.7 ± 2.5	9.5 ± 3.7
+3	26 ± 0	29.7 ± 11.2	25.7 ± 8.1	11.5 ± 3.5	13 ± 3	11.8 ± 4.5
ANOVA: P value	*0.032**	*<0.001**	*<0.001**	*0.036**	*<0.001**	*<0.001**

* P values <0.05 considered as statistically significant

4. Discussion

Critically ill patients are the most challenging and important priority of treating physician. Predicting outcome of critically ill patients in a systematic way, depending on definite objective data is an integral part of the quality of care in ICU. Conventionally, ICU physicians had been able to distinguish survivors and non-survivors based on their clinical experience. The development of severity of illness scoring system had altered the approach into a more objective and reliable process. Illness severity scoring systems have become important tools for studying patient outcomes [29]. Furthermore, to assessing the prognosis, the severity of illness scoring systems also aids in resource

allocation and compare the performance of ICUs. The predictive accuracy of the severity of illness scoring systems changes over time [30].

Table 3: Outcome wise comparison of Proteinuria levels, APACHE II and SOFA scores

Variables \ Day	Admission Day 1		Admission Day 3		Admission Day 5	
	Survivor	Non-survivor	Survivor	Non-survivor	Survivor	Non-survivor
Proteinuria	n = 81	n = 15	n = 81	n = 15	n = 81	n = 15
Nil / Trace	47 (58.0)	5 (33.3)	44 (54.3)	2 (13.3)	47 (58.0)	0
+1 to +3	34 (42.0)	10 (66.7)	37 (45.7)	13 (86.7	34 (42.0)	0
P value	0.078		0.004*		--	
APACHE II score (Mean ± SD)	20.1 ± 8.1	23.9 ± 7.9	19.3 ± 8.5	26.1 ± 8.4	18.0 ± 10.2	--
P value	*0.089*		*0.060*		--	
SOFA score (Mean ± SD)	7.6 ± 2.8	7.3 ± 2.0	7.9 ± 3.0	9.3 ± 2.2	7.6 ± 3.8	--
P value	*0.668*		*0.078*		--	

* P values <0.05 considered as statistically significant

Current observational cross-sectional study conducted in 96 critically ill patients admitted to MICU for studying the correlation between proteinuria levels and mortality risk with mean age of patients was 47.1 ± 19.2 years (range 15–92 years). Compared to current study, higher mean age was found in a study done by Chen et al., [31] (67.5 ± 13 years), Godijn et al., [32] (68.6 ± 11.1 years), Ashok and Mushtaque [33] (62.4 ± 9.2 years) and Ho [34] (53.9 ± 19.1 years), while lower median age was found by Bhadade et al., [35] (35 years). In present study, female dominance noted with male – female ratio of 1:1.1. Contrasting to current study male predominance was found in study conducted by Chen et al., [31] (2.8:1), Godijn et al., [32] (2.5:1), Bhadade et al., [35] (2.1), Ashok and Mushtaque [33] (1.8:1), Ho [34] (1.6:1)

In present study, 60.4% patient had proteinuria at 1st day, at 3rd day and 45.7% at 5th day. While percent of patients with grade +3 proteinuria were increased from day 1 to day 5 (2.1% vs 11.1%), however, in other categories of proteinuria, percent of patients were decreased from day 1 to day 5 (Table 1). A study by Chen et al., [31] had found proteinuria in 51.1% patients.

The APACHE II scoring system was simplified version of the original APACHE system and widely used as ICU prognostic scoring model. It had been an accurate measurement of patient severity and associates strongly with outcome in critical patients [25]. In current study, mean APACHE II scores was decreases significantly from 3rd day to 5th day and from 1st day to 5th day ($p<0.05$) (Table 1). Additionally, mean APACHE-II scores were significantly increasing with raising grades of proteinuria on 1st day, 3rd day and 5th day of admission ($p<0.05$) (Table 2). Moreover, mean values of APACHE II scores had non-significant relationship with outcome on 1st day and 3rd day of admission ($p>0.05$) (Table 3).

A study done by Godijn et al., [32] had found mean values of APACHE II score among all patients was 20.5±6.3 at 24 hours of ICU stay that was almost same to current study. While KM Ho [34] had found mean APACHE II score was 17 ± 7.7 among all patients and APACHE II scoring was significantly lower among survivors (15.4 ± 6.5) compared to non-survivors (26.2±7.9, $p<0.05$). Another study by Varghese et al., [36] had found that mean admission APACHE II score

was 19.4 ± 8.9, and Both APACHE II and IV scores were significantly higher among non-survivors compared to survivors (p<0.001). A study by Chen et al., [31] had noted that mean APACHE III scoring was significantly higher among proteinuria patients (44.8±25.5) compared to patients without proteinuria (27.4±15.9; p<0.05). In a study done by Polita et al., [37] had found that non-survivors had significantly greater mean APACHE II (10.7 ± 7.8) compared to survivors (3.9 ± 4.5, p<0.002).

SOFA score on first few days of ICU admission was good indicator of prognosis. Both mean and highest SOFA scores were particularly useful predictors of outcome. Independent of initial score, an increase in SOFA score during first 48 hours in ICU predicts around 50% mortality rate [38]. Mean SOFA score had highest sensitivity and specificity in prediction of ICU mortality hence, it was valuable indicator to better predictions of mortality and morbidity rate in ICU patients, which could lead to appropriate health care and therapeutic interventions in these patients [39]. In present study, SOFA scores was significantly increases from admission to 3rd day (p<0.05) but decreases non-significantly from 3rd day to 5th day (p>0.05) (Table 1). Additionally, mean values of SOFA scores were significantly increasing with raising grades of proteinuria on 1st day, 3rd day and 5th day of admission (p<0.05) (Table 2). Furthermore, mean SOFA had non-significant relationship on 1st day and on 3rd day of admission with outcome (p>0.05) (Table 3).

A study by Kumar et al., [40] had found that mean SOFA score had shown significantly increasing trend in first week, mostly on first 3 days, which signifies progressive organ dysfunction among non-survivors. SOFA score on day 1 was significantly high amongst non-survivors comparing to survivor was (9.33 V/s 6.62, p<0.001). Though, Godijn et al., [32] had found mean values of SOFA score among all patients was 5±2.9 at 24 hours of ICU stay that was lower to current study. Similar to present study, Ashok and Mushtaque [33] had found that highest SOFA score was 7.4 within first 24 hours of ICU admission. The median SOFA scores was in Bhadade et al., [35] study was 6, while mean SOFA score was higher among medical ICU patients (7.1± 3.5) compared to surgical ICU patients (4.9±2.2) [32].

In a study of Chen et al., [31], mean SOFA score was significantly higher among patients with proteinuria (3.6 ± 3.2) compared to patients with no-proteinuria (2 ± 2.5; p<0.05). A study by Jain et al., [14] had found that maximum SOFA score among survivors was significantly lower comparing to non-survivor (3.92 ± 2.17 vs 8.9 ± 3.45) that indicating strong correlation of mortality with SOFA scores on day 1. KM Ho [34] had found lower mean SOFA score on day 1 of admission (6.3 ± 3.8) and mean SOFA scoring at 24 hours of admission was significantly lower among survivors compared to non-survivors (5.6 ± 3.4 vs 9.9 ± 4, p<0.05). Vishal Gupta et al., [41] had also found positive correlation between mortality and SOFA score at admission and at 48 hours. SOFA scoring system for every individual disease group might give prognostic guidance for that individual disease. In short SOFA score was very useful in predicting mortality in critically ill patients, since there was strong correlation between rise in the score and mortality in all the stages of admission [42]. SOFA score thus could be effectively used as predictive scoring system for critically ill elderly patients.

Proteinuria was increasing with increasing ICU stays and it also increasing with among non-survivor patients. Proteinuria, APACHE-II and SOFA scores at admission could be used to quantify degree of dysfunction/failure and triage of patients into risk categories for further management. Highest APACHE-II and SOFA scores can identify critical point at which patient exhibit highest degree of organ dysfunction at MICU stay. Current study had also found positive relationship of proteinuria with APACHE-II and SOFA scores among MICU admitted patients.

Author contribution

All authors read and approved the final version of article.

Conflict of interest

The Authors report no relationships, which could be considered as conflict of interest.

Ethical declarations

All Test cases were used in accordance with the requirements of the Rohilkhand Medical College & Hospital, Pilibhit Bypass Road, Bareilly (U.P.) Pin-243006 (registered ethical allowance).

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