Original Article

Microalbuminuria: A Predictor of Outcome in Critically ill Patients in Intensive Care Units.

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Abstract:

Background: *Diffuse endothelial dysfunction in physical, chemical or infectious insult to the host leads to an increase in systemic capillary permeability. The renal component manifests as Microalbuminuria. The degree of Microalbuminuria correlates with the severity of the acute insult and the quantification of which may serve to predict outcome in critically ill patients.*

Objectives: *To evaluate whether the degree of Microalbuminuria could predict outcome in critically ill patients or not.*

Settings and Study design: *This cohort study was carried out in the 20 bed mixed Medical-Surgical Intensive Care Unit of Dhaka Medical College Hospital. A total 60 patients were purposively recruited for this study. In our study, we included all adult critically ill patients aged 18 years or more admitted in ICU after fulfilling the criteria of critically ill patients and who stayed for more than 24 hours. Patients with pregnancy, menstruation, anuria, macroscopic haematuria, pre-existing kidney disease, were excluded. Spot urine samples were collected by ICU nurses at 24 hrs of admission, for the quantification of Albumin Creatinine Ratio, which was referred to as ACR. The outcome of the patient was classified as death and discharge / survival. Maximum follow up was done for 15 days. Patients discharged within this 15 days, were considered as survival.*

Results: *Patients were divided into two groups, Group-I: subjects (exposed): Patients having Microalbuminuria. Group-II: control (unexposed): Patients having no Microalbuminuria. In this study, Relative Risk was calculated for risk measurement and to assess the strength of association between the patients having Microalbuminuria and outcome and the calculated relative risk was 2.08. It indicates that the presence of Microalbuminuria is a risk factor for the critically ill patients. Chi-square test was used to compare categorical outcomes and for hypothesis testing. The test statisticis11.94 and p=<0.001.So, our study result supports the hypothesis that Microalbuminuria predicts the outcome in critically ill patients.*

Conclusion: *It was observed that the presence of Microalbuminuria at 24 hours of ICU admission is a predictor of poor outcome in critically ill patients. Absence of Microalbuminuria at 24hrs of admission may help to predict survival in the ICU. So the study concludes that the Microalbuminuria would provide a rapid, simple, inexpensive bedside test to identify patients who may benefit from appropriate early therapeutic strategies. It may prevent further capillary leak and hence the onset of multi organ failure and death.*

Key Words: *Microalbuminuria, Critically ill patients, Intensive care units, mortality, outcome.*

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Introduction:

Recognition, assessment, and management of critically ill patients are the fundamental to critical care. The principles of intensive care management are the simultaneous assessment of severity of illness and the stabilization of critically ill patients, who are at imminent risk of death due to some potentially life threatening illness. Suboptimal attention to either resuscitation or diagnostic processes result in ill outcomes and increased mortality in Intensive care units.

For this reason, a reliable method for prediction of outcome which patients benefit most from intensive care is a crying need. Several scoring systems based on the severity of physiological derangements and preexisting health status have been proposed, such as the Acute Physiology and Chronic Health Evaluation (APACHE) & Therapeutic Intervention Scoring System(TISS), Sequential Organ Failure Assessment Score(SOFA), Simplified Acute Physiology Score (SAPS-II) but none is satisfactory and they are cumbersome. They require input of a large number of variables derived from the patient's history, physical examinations and initial laboratory data. But, sensitive, inexpensive, dynamic prognostic markers which can generate rapid & reliable results are therefore desirable in the ICU settings. As it allow the planning of early aggressive therapeutic interventions, optimum resource allocation & appropriate counseling of the family.

The critical illness is more often characterized by the inflammatory response that is triggered by a physical, chemical or infectious insult to the host. It generates a variety of noxious substances e.g. proteolytic enzymes, reactive oxygen metabolites which damages the host defense mechanism. When the inflammatory injury once starts, becomes a self sustaining process & triggers more & more tissue damages. This severe &sustained inflammatory reaction induces rapid & profound changes in the endothelium resulting in loss of barrier integrity leading to systemic capillary leak in vascular beds. In the kidneys this manifests as altered glomerular permeability culminating in increased renal albumin excretion in the urine.

Microalbuminuria is a reflection of this capillary leak due to endothelial dysfunction. Micro-albuminuria describes is a clear sign of glomerular injury, &this can identify very early stages of such insult. Screening for Microalbuminuria is usually performed by one of three methods. These are as follows-

1. Measurement of total urine volume in 12 or 24 hour collection,
2. Measurement of the Albumin-Creatinine ratio in morning or random sample,
3. Measurement of urine albumin in morning urine.

The 24hrs collection of urine is time consuming and thus expensive and requires highly motivated patients, careful information and it is often difficult to perform.

But the measurement of the Albumin-Creatinine ratio in morning or random sample is more convenient and easier.

The Microalbuminuria can be expressed as urinary albumin –creatinine ratio (ACR).The random urine sample can estimate Urinary Albumin-Creatinine ratio (ACR) and this value was taken for our study purpose.

Urine albumin can be analyzed with HemoCue method. Urine albumin is also measured by nephelometry by using a Behring Bn ProSpec analyser(Dade Behring).

The urine creatinine can be analyzed with a modified Kinetic –Jeffe reaction on an Architect Ci8200 analyzer & reported as S.I. units. The level of Microalbuminuria values between 3-30 mg /mmol (30-300microgram/mg).

We surmised that, Microalbuminuria(ACR) would reflect the degree of ongoing endothelial dysfunction .The level of micro albumin in urine also reflect the status of endothelial function after effective protocol directed therapeutic intervention like fluid resuscitation, antibiotics, inotrope & vasopressor use, tight glycemic control. Thus, the Microalbuminuria could predict the outcome.

Materials and Methods:

This cohort study was carried out in a 20 bed mixed Medical-Surgical Intensive Care Unit in the Department of Anesthesia, Analgesia and Intensive Care Unit of Dhaka Medical College Hospital, Dhaka over a period of 24 months starting from January 2012 to December 2013. Prior to the commencement of this study, the research protocol was submitted to the Ethical Review Committee of Dhaka Medical

College Hospital and was approved. Study population was the patients who were admitted in ICU, DMCH. All adult critically ill patients aged 18 years or more admitted in ICU having any one of the criteria of critically ill patients & patients of ICU who stayed for more than 24 hours were included in this study.On the other hand patient staying in ICU<24hours, patients with anuria, patients with pregnancy and menstruation, patients receiving nephrotoxic drugs, patients with urologic trauma resulting in frank hematuria &patients with pre-existing Kidney Disease (Serum creatinine ^{3} 2.0 mg/dl)were excluded.

A total number of 60 patients were prospectively divided into two groups of 30 patients each. Patients having Microalbuminuria constituted group-I(exposed) while those having no Microalbuminuria constituted Group-II (unexposed).

Study Procedure:

Data were collected using a structured questionnaire containing all the variables interest. The questionnaire included age, sex, diagnosis, clinical classification (Medical/Surgical), and provisional diagnosis. Co-morbid conditions such as diabetes, hypertension, bronchial asthma, COPD and chronic kidney disease, Glasgow Coma Scale, blood pressure, temperature, heart rate, respiratory rate and some relevant investigations, were also included.The Albumin- Creatinine ratio was done from urine sample. Materials and instruments required to perform the study were arterial blood gas analyzer, blood sample and urine sample. Data were collected during the first 24 hours following ICU admission. Patients were selected after fulfilling the inclusion and exclusion criteria. Spot urine samples were collected by ICU nurses at 24 hours of admission & were received in the biochemistry lab. For quantification of the Microalbuminuria, Albumin-Creatinine ratio (ACR) was measured. Urine albumin was measured by nephelometry by using a Behring Bn ProSpec analyser(Dade Behring).The urine creatinine was analyzed with a modified Kinetic –Jeffe reaction on an Architect Ci8200 analyzer & reported as S.I. units.Data were collected, documented and laboratory data were collected by the investigator.The quantity of Microalbuminuria was assessed from the Albumin-Creatinine Ratio (ACR) value at 24 hours of ICU admission of critically ill patients. Patients were divided into two groups,

Group-I: subjects (exposed): Patients having Microalbuminuria.

Group-II: control (unexposed): Patients having no Microalbuminuria.

Statistical analysis:

Collected data were analyzed using SPSS (Statistical Package for Social Sciences) for windows, version 21.0 (SPSS, Team Eqx, 1337).The qualitative data were expressed as frequency and percentage&the quantitative data were expressed as mean and standard deviation. Relative Risk was calculated to assess the strength of association between the patients having Microalbuminuria and outcome and for risk measurement. Non -parametric Chi-square test was done among the two groups of patients with and without Microalbuminuria for hypothesis testing that Microalbuminuria predicts the outcome in critically ill patients.

Results:

Table I *Age distribution between groups*

Demographic variables	Group		p-value
	Group-I(with Microalbum-inuria) (n=30)	Group-II(without Microalbum-inuria) (n=30)	
Age (years)			
<30	4(13.33%)	6(20%)	0.36
>30	26(86.78%)	24(80%)	
Mean±SD	40.67±17.92	39.93±11.77	

*Student's T-test was done to analyze the data and data were presented as Mean and ±SD.

Table II *Sex distribution between groups*

Sex	Group-I (with Microalbuminuria) (n =30)		Group-II (without Microalbuminuria) (n =30)	
	Frequency	Percent	Frequency	Percent
Male	6	20	10	33.33
Female	24	80	20	66.67

Table-III *Comparisons of the criteria of critically ill patients between two groups:*

Variables	Group		p-value
	Group-I (Mean±SD)	Group-II (Mean±SD)	
Glasgow Coma scale	10±2	11.25±1.45	.10^{NS}
Temperature	101.4±3.21	99±2.47	.05^{NS}
Mean arterial pressure	106.26±7.11	85.55±6.56	.03^{NS}
Heart rate	130±15.03	95.68±13.79	.02^{NS}
Respiratory rate	35.67±1.11	24±0.814	.02^{NS}

*Student's T-test was done to analyze the data and data were presented as Mean and ±SD.

Table IV *The Co-morbid conditions among the patients of group-I and group-II*

Co-morbid conditions	Group-I (with Microalbuminuria) (n =30)		Group-II (without Microalbuminuria) (n =30)	
	Frequency	percent	Frequency	Percent
Hypertension	12	40	8	26.67
Diabetes	8	26.67	6	20
Others	6	20	4	13.33
None	4	13.33	12	40

Table-V *The medical and surgical cases among the patients of group-I and group-II*

	Group-I (with Microalbuminuria) (n =30)		Group-II (without Microalbuminuria) (n =30)	
	Frequency	percent	Frequency	Percent
Medical	21	70	10	33.33
Surgical	9	30	20	66.67

Table-VI *Relation between Microalbuminuria and outcome of patients with basic risk measurement.*

Microalbuminuria	Outcome Non-survivors	Survivors	Total	Relative Risk
Yes	25(83.33%)	5(16.67)	30	
No	12(40%)	18(60%)	30	2.08
Total	37	23	60	

Table-VII *Chi-square test*

Microalbuminuria	Outcome Non-survivors	Survivors	Total	χ^2(chi-square)	p-value
Yes	25	5	30		
No	12	18	30	11.94	<.001^s
Total	37	23	60		

Discussion:

In this study demographic variable in the term of age showed almost similar and there were no significant difference between group-I and group-II which correlates the findings of the prospective, observational study of RR Bhadade et al. (2014) which was done on 163 critically ill patients. The study also observed the sex distribution between group-I and group-II. There were 6 males and 24 females in group-I which constitutes 20% and 80% respectively .In group-II there were 10 were male and 20 were female which constitutes 33.33% and 66.67% respectively. The findings were almost similar.

In this study, the criteria of critically ill patients between two groups were observed (Glasgow Coma scale, temperature, mean arterial pressure, heart rate, respiratory rate) and there were no significant difference between group-I and group-II in terms of Glasgow Coma scale and temperature (p=0.101and p=.052 respectively).But there were significant difference between group-1and group-2 in terms of mean arterial pressure, heart rate, respiratory rate (p=.032, p =.021, p=.026 respectively).

The Co-morbid conditions among the patients of group-I and group-II were observed. These demonstrate that the co-morbid condition was significantly higher in the patients of group-I than that of group-II but in contrast to our study result, RR Bhadade et al. (2014) found no significant difference between two groups, in their study. In our study, the medical and surgical cases among the patients of group-I and group-II were observed and it was observed that the medical cases were more in group-I and surgical cases were more in group-II. Our study result supports the findings of the study conducted by Mann JF et al. (2004). They also found similar result.

In this study, Relative Risk was calculated for risk measurement and to assess the strength of

association between the patients having Microalbuminuria and outcome and it was observed that relative risk was 2.08 which proves the association between the Microalbuminuria and outcome and indicates that the presence of Microalbuminuria is a risk factor for the critically ill patients.

In to our study, our result supports the findings of the study conducted by Mann JF et al. (2004). They found that Microalbuminuria is a continuous risk factor for critically ill patients. This study was done on 9043 patients with Microalbuminuria. Relative risk was 2.03 at 95% confidence interval.

The result of our study also supports the findings of the study conducted by Gerstein HC et al. (2001). They found that any degree of Microalbuminuria is a risk factor for critically ill patients (Relative risk was 1.83 at 95% confidence interval.) Abid et al. (2001) had also found a higher mortality among patients with increasing Microalbuminuria levels. In the past, studies done by Gosling et al. (2003), Thoevska et al. (2003) and Gopal et al. (2006) also found Microalbuminuria as a good marker in the prediction of mortality. Microalbuminuria is a non-invasive, inexpensive, and ready to-use bedside screening test to identify the patients who are critically ill (Positive predictive value[PPV 88%]). Furthermore, the findings of 93% sensitivity and 71% specificity of 6 hours of ACR appears comparable to the reported mean percentage sensitivity of 85% and specificity of 83% of PCT. and 69%,and 61%,respectively.of CRP, in differentiating infected individuals from uninfected controls. The ACR test results can be made available as early as 30 minutes.

Chi-square test was done for hypothesis testing that Microalbuminuria predicts the outcome in critically ill patients. The test statistic was 11.94 and p was <0.001. So, the alternate hypothesis accepted that the Microalbuminuria predicts the outcome in critically ill patients. The interpretation of Chi-square test also supports the findings of the prospective, observational study of RR Bhadade et al.(2014 which was conducted on 163 critically ill patients. Significantly higher levels of Microalbuminuria were found among the patients and the level decreased in survivors after 24 hours. Persistence of high level of Microalbuminuria over 24 hours was found to be a predictor of poor outcome. A high level of Microalbuminuria at 24 hours and increasing trend of Microalbuminuria also predicted mortality better than APACHEII and SOFA scores.

So, the overall results of our study suggest that the high level of Microalbuminuria at 24 hours was found to be a predictor of poor outcome. A high level of Microalbuminuria at 24 hours predicts mortality in critically ill patients and the absence of significant Microalbuminuria at 24 hours of admission may help to predict survival in the ICU.

Limitations:

This was a single centre study. As the sample size was small, the findings derived from study cannot be generalized to reference population, it was carried out in an adult Intensive Care Unit (ICU). So pediatric group of population was not included. The speed and magnitude of the renal permeability response to indirect injury and its association with outcome suggest that, measurement of Microalbuminuria can play an important role in the early identification of patients at increased risk of developing Multi system organ failure & as the number of patients studied was small, further studies in larger numbers of heterogeneous patients are recommended.

Conclusions:

It was observed that the presence of Microalbuminuria at 24 hours is a predictor of poor outcome in critically ill patients. Absence of Microalbuminuria at 24hrs of admission may help to predict survival in the ICU. So the study concludes that the Microalbuminuria would provide a rapid, simple, inexpensive test to identify patients who may benefit from appropriate early therapeutic strategies. It may prevent further capillary leak and hence the onset of multi organ failure and death.

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