MICROALBUMINURIA PREDICTS NEED FOR AND DURATION OF MECHANICAL VENTILATION IN SEVERE TRAUMA

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Abstract

Purpose: to determining the incidence and the presence of a relationship between microalbuminuria and need for as well as duration of mechanical ventilation in trauma patients admitted to intensive care unit (ICU) and compare its predictive value with base deficit and amount of fluids received over the first 24 hours of ICU admission.
Design: a cross sectional comparative study conducted over the period between August 2014 and March 2015.
Setting: trauma intensive care unit (ICU) of Mansoura Emergency Hospital.
Patients: sixty two severely traumatized patients requiring mechanical ventilation.
Methods: Patients were categorized by duration of mechanical ventilation to group (A) (≤7 days) or group (B) (>7 days). The amount of fluids received over the first 24 hours of ICU admission was recorded. Furthermore, serial Base Deficit (BD) on admission, after 12 hours and 24 hours of admission were recorded. Also, serial spot urine micro-albumin-creatinine ratios (ACR) on admission (ACR1) and at 24 hours after admission (ACR2) were measured. Trend of Micro-albuminuria was assessed from change of Albumin Creatinine Ratio-1 (ACR1) to Albumin Creatinine Ratio-2 (ACR2). The difference between those values, delta Albumin creatinine ratio (Δ ACR), was calculated.
Results: There was no statistically significant difference between the two studied groups as regard amount of fluids received over the first 24 hours of ICU admission and base deficit. While, (62.9%) of patients had microalbuminuria on admission and 72.6% became microalbuminuric after 24 hours of ICU admission. Moreover, there was statistically highly significant difference between the two studied groups as regard Glasgow Coma Score (GCS), Revised Trauma Score (RTS) values and Delta Albumin Creatinine Ratio (Δ ACR).
Conclusion: Glasgow Coma Score (GCS), Revised Trauma Score (RTS) value and Δ Albumin Creatinine Ratio (Δ ACR), predicted need for and duration of Mechanical Ventilation (MV) >7days.

Keywords: Severe trauma, mechanical ventilation, fluid therapy, base deficit, microalbuminuria, Glasgow coma score, revised trauma score.

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Introduction

Severe trauma is often life threatening and usually presents as an emergency, requiring immediate surgical intervention and or intensive care or both [(1)].

The Revised Trauma Score (RTS) was introduced by Champion *et al*. [(2)].It is a physiologic scoring system that uses blood pressure, Glasgow Coma Scale (GCS), and respiratory rate to quantify the degree of physiological derangement to arrive at scores that correlate with clinical outcomes. A lower score indicates a higher severity of injury.

Many different clinical conditions can lead to respiratory failure and mechanical ventilation[(3)].The length of time a patient remains in need for mechanical ventilation depends on the cause and severity of respiratory failure [(4)].Many clinically measured parameters and calculated laboratory variables have been investigated as possible predictors of mechanical ventilation dependency and outcome[(5)].

Shock is a predominant risk factor for multiple organ dysfunction syndrome (MODS) and shock resuscitation is an obligatory early intervention. Because both under and over resuscitation contribute to the pathogenesis of MODS. Elevated BD occurs before fall in blood pressure to classic "hypotension" levels and values ≤ -6 mEq/L identifies patients that require early, massive transfusion, and are at risk for adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF) with higher mortality [(6,7)].

Trauma initiates a systemic response that activates some types of target cells (macrophages, leukocytes, lymphocytes) and releases well-known inflammatory mediators (cytokines). These two mechanisms provoke the inflammatory response commonly observed in critically ill patients [(8,9)]. A very early feature of inflammation is increased capillary permeability to plasma proteins, which occurs within a few minutes of injury and usually returns to normal within 6 to 12 hours [(10)].

Assessment of alterations in endothelial permeability, such as the presence of microalbuminuria, may thus be a useful, early, and simple indicator of patients at risk for development of acute respiratory failure and multiple organ failure [(11)].

The degree of albuminuria is dependent, in part, on the intensity of the inflammatory responses and on baseline integrity of the glomerular capillary wall and can be reliably indexed with a spot urine albumin-creatinine ratio (ACR) [(12)]. It adjusts for variable urine concentrations among patients and obviates the need for a 24 hours or timed urine collection [(13)]. Such low rates of albumin excretion are termed microalbuminuria[(12)].

Micro-albuminuria, defined as 30–300 mg/day of albumin excretion in the urine, in trauma patients, a transient increase in the urinary excretion of proteins and albumin was shown to occur within 4 hours of the acute event. It recurs if sepsis complicates the clinical course [14].

The need for and the duration of MV, which are indicators of serious health complications and significantly affect healthcare costs, are thus valid measures for research [15,16].

The present study is designed to determine the incidence and presence of a relationship between microalbuminuria and need for as well as duration of mechanical ventilation in trauma intensive care unit (ICU) patients and compare its predictive value with base deficit and amount of fluids received over the first 24 hours of ICU admission.

Materials And Methods

This study was conducted on (62) adult patients (54Males and eight Females), according to sample size calculation, who were admitted to the Intensive Care Unit (ICU) at Mansoura Emergency Hospital, over the period from August 2014 to March 2015 with a diagnosis of severe trauma according to the Revised Trauma Score (RTS) [2] and their ages ranged from 18 to 71 years old.

Inclusion criteria:

All adult severely traumatized patients with Revised Trauma Score (RTS = 3 - 10) were included in the study.

Patients were categorized according to the duration of mechanical ventilation (MV) into two groups [17, 18, 19, 20]:

Group (A): Non prolonged MV group (MV≤ 7 days) included 31 patients.

Group (B): Prolonged MV group (MV> 7 days) included 31 patients.

Exclusion criteria:

- Patients aged less than 18 years.
- Pregnant females.
- Patients who suffered burn trauma.
- Patients with anuria.
- Overtly bloody urine.
- Being on renal replacement therapy.
- Existing chronic renal disease (serum creatinine level ≥ 2 mg dl).
- Urinary tract infection.
- Inability to measure urine albumin due to hyperpigmentation of the urine specimen.
- Patient with a diagnosis of type 1 or type 2 diabetes mellitus.
- Patients receiving nephrotoxic drugs.

All patients included in the study were subjected on admission to the followings:

1. Complete history taking.

2. Complete physical examination.
3. The following scores were recorded on admission:
    - Revised Trauma Score (RTS) [2]: It was scored from the first set of data obtained on the patient, and consists of Glasgow Coma Scale, Systolic Blood Pressure and Respiratory Rate. Patients with a total RTS score of 12 were categorized as minor injuries, 11 moderate, and 10‑3 severe.
    - Glasgow Coma Scale (GCS) [21]: The GCS is scored between 3 and 15. 3 being the worst, and 15 the best. It is composed of three parameters: Best Eye Response, Best Verbal Response, and Best Motor Response.
4. Causes for initiation of mechanical ventilation (MV) (postoperative ventilation, hemodynamic, respiratory, and neurologic disorders) were recorded.
5. The following investigations were done to all patients:
    - Measurement of Arterial blood gas (ABG) and Base deficit (BD): on admission, after 12 hours and after 24 hours by heparinized blood samples using ABL 700 supplied by Radiometer (Copenhagen) (Denmark).Mean Base Deficit (Mean BD) was then calculated.
    - Spot Urine samples were collected on admission and after 24 hours for:
        - Urinary creatinine: was measured on Dimension Expand Plus (Siemens Diagnostic – USA) using its commercial kits.
        - Urinary microalbumin: was measured by Enzyme Linked Immunosorbent Assay (ELISA) kits supplied by ORGENTEC Diagnostika (Carl-Zeiss-Straße 49 – 51, 55129 Mainz, Germany).
    - Albumin Creatinine Ratio (ACR) was then calculated on admission (ACR1) and after 24 hours of ICU admission (ACR2). Micro-albuminuria was defined by Albumin Creatinine Ratio values between 30 and 300 mg/g. Trend of Micro-albuminuria was assessed from change of Albumin Creatinine Ratio-1 (ACR1) to Albumin Creatinine Ratio-2 (ACR2). The difference between those values, delta Albumin creatinine ratio (Δ ACR), was calculated.
6. Outcome variables:

    Each patient was followed through his ICU stay for seven days and the following outcomes were recorded:

    - Need for mechanical ventilation.
    - Duration of mechanical ventilation.
7. All patients were managed according to the same protocol as regard:
    - Fluid management [22].
    - Ventilatory management.

Statistical Analysis

Data were analyzed with SPSS version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test (χ^2).

Continuous variables were presented as mean ± SD (standard deviation) for parametric data and Median for non-parametric data. The two groups were compared with Student t test (parametric data) and Mann–Whitney test (non parametric data). Spearman correlation used for correlation between continuous non parametric data. Logistic regression analysis was performed to identify which independent predictors might have significant influence. Sensitivity and specificity at different cutoff points were tested by Receiver-operating characteristic (Roc) Curve.

Level of significance

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value).

The results were considered:

- Significant when the probability of error is less than 5% ($p \leq 0.05$).
- Non-significant when the probability of error is more than 5% ($p > 0.05$).
- Highly significant when the probability of error is less than 0.1% ($p \leq 0.001$).

The smaller the p-value obtained, the more significant are the results.

Results

All patients were mechanically ventilated soon after intensive care unit (ICU) admission. Neurologic cause for initiation of mechanical ventilation was the most common in group (A) and group (B) representing 61.3%, 74.2% respectively followed by Respiratory cause representing 41.9%, 45.2% respectively.

Glasgow coma score (GCS) and Revised trauma score (RTS) value were lower in group (B) than group (A).

As regard amount of fluids received by the patients over first 24 hours after admission to ICU as well as mean base deficit, there was no statistically significant difference between the two studied groups (p value >0.05).

Table (1) shows no significant difference between the two groups as regard amount of fluids received by the patients over first 24 hours after admission to ICU (p value >0.05).

Table (1): amount of fluids received over first 24 hours between all studied groups (n = 62)

Items	Group (A) n = 31		Group (B) n = 31		p-value	Student *t* test
	Mean ± SD	Min-Max	Mean ± SD	Min-Max		
Fluids	3745.3±568.84	3000-4900	3960±681.71	3000-5360	P=0.183	t=1.346

n = Number, SD=Standard Deviation, Min=Minimum, Max=Maximum, t=Student t test, p < 0.05 is significant.

Table (2) shows no significant difference between the two groups as regard Mean Base Deficit (Mean BD), (p value >0.05).

Table (2): Mean Base Deficit between all studied groups (n = 62)

Items	Group (A) n=31		Group (B) n=31		p-value	Mann–Whitney test
	Median	Min-Max	Median	Min-Max		
Mean BD	-4.70	-20.40 :1.40	-5.10	-18.10 : 2.20	p=0.811	Z= .239

BD=Base Deficit, Min=Minimum, Max=Maximum, Z= Mann–Whitney test, n=Number, p < 0.05 is significant.

On admission, 62.9% were microalbuminuric (ACR1=30-300mg/g) and 72.6% became microalbuminuric after 24 hours of ICU admission. There was no statistically significant difference between the two groups as regard ACR1 and ACR2 (p value >0.05) while there was statistically significant difference between the two groups as regard Δ ACR (p=0.002). Δ ACR is lower in group (B) than group (A). So, Δ ACR is better in prediction of Mechanical Ventilation (MV) >7days than ACR1 and ACR2.

Table (3) shows overall incidence of albuminuria on admission (Albumin Creatinine Ratio (ACR1)) and after 24 hours (Albumin Creatinine Ratio (ACR2)) among all studied groups.

Table (3): Overall incidence of albuminuria on admission and after 24 hours among all studied groups (n = 62)

Items	Total (n=62)					
	Normoalbuminuria		Microalbuminuria		Macroalbuminuria	
	n	%	n	%	n	%
ACR1(on admission)	8	12.9	39	62.9	15	24.2
ACR2(after 24 hours)	8	12.9	45	72.6	9	14.5

ACR1=Albumin Creatinine Ratio on admission, ACR2= Albumin Creatinine Ratio after 24 hours, n=Number.

Table (4) shows no significant difference between the two groups as regard ACR1 and ACR2 (p value >0.05) while there was significant difference between the two groups as regard Δ ACR (p=0.002). Δ ACR was lower in group (B) than group (A**).**

Table (4): Comparison of Albumin Creatinine on admission, after 24 hours and Δ Albumin Creatinine Ratio between all studied groups (n = 62)

Items	Group (A) n=31		Group (B) n=31		p-value	Mann–Whitney test
	Median	Min-Max	Median	Min-Max		
ACR1(on admission)	173	14.70-1074	76.70	11.30-1838	p=0.062	Z= 1.865
ACR2(after 24 hours)	90.70	3-685	102	12-4951	p=0.730	Z=.345
Δ ACR	29	-414 : 909.80	-12.80	-3791 : 469	p=0.002*	Z= 3.041

n=Number, ACR1= Albumin Creatinine Ratio on admission, ACR2= Albumin Creatinine Ratio after 24 hours, Δ ACR= difference between ACR1 and ACR2, Min=Minimum, Max=Maximum,Z= Mann–Whitney test, $p < 0.05$ is significant.

By using ROC curve, the sensitivity and Specificity of Δ ACR at cutoff point 130.35was 90.3% and 35.5% respectively. Also, the sensitivity and Specificity of Glasgow Coma Scale (GCS) at cutoff point 9 was 93.5% and 39% respectively. While, the sensitivity and Specificity of Revised Trauma Score (RTS) values at cutoff point 6.02 was 96.8% and 26% respectively.

Table (5) shows the cut off values of Δ Albumin Creatinine Ratio (Δ ACR), Glasgow Coma Scale (GCS) and Revised Trauma Score (RTS) values in addition to their sensitivity and specificity respectively.

Table (5): cutoff values of Δ Albumin Creatinine Ratio, Glasgow Coma Scale, Revised Trauma Score value for prediction Mechanical Ventilation (MV) > 7days

Item	AUC	95% Confidence Interval		Cutoff point	Sensitivity	Specificity
		Lower Bound	Upper Bound			
Δ ACR	0.725	0.598	0.851	130.35	90.3%	35.5%
GCS	0.795	0.686	0.904	9	93.5%	39%
RTS value	0.757	0.638	0.875	6.02	96.8%	26%

ACR=Albumin Creatinine Ratio, Δ ACR= difference between ACR1 and ACR2, GCS=Glasgow Coma Scale, RTS=Revised Trauma Score, AUC= area under the receiver operating characteristic curve.

By using logistic regression analysis, Glasgow Coma Scale (GCS<9), Revised Trauma Score (RTS>6.02) value and Δ Albumin Creatinine Ratio (Δ ACR<130.35) were significant predictors of Mechanical Ventilation (MV) >7days. [(p-value 0.007, 0.032, 0.022) respectively and (OR (95%CI) were 9.158(1.840-45.579), 10.435 (1.217-89.461), 5.133 (1.266-20.809)) respectively].

Of them, Glasgow Coma Scale (GCS) was the best significant predictor of Mechanical Ventilation (MV) >7days. P-value 0.007 and OR (95%CI) was 9.158 (1.840-45.579) and accounted for 74.2% of the variance of Mechanical Ventilation (MV) >7days (Constant= 3.13, Model χ^2 = 14.79, p=0.002).

Table (6) shows that, by using logistic regression analysis, Glasgow Coma Scale (GCS<9), Revised Trauma Score (RTS>6.02) value and Δ Albumin Creatinine Ratio (Δ ACR<130.35) are significant predictors of Mechanical Ventilation (MV) >7days.of them, Glasgow Coma Scale (GCS) is the best significant predictor of Mechanical Ventilation (MV) >7days and accounts for 74.2% of the variance of Mechanical Ventilation (MV) >7days.

Table (6): Logistic regression for prediction of Mechanical Ventilation >7 days

Independent predictors	B	P-value	OR	95 % C.I for OR	
				Lower	Upper
GCS (<9)	2.215	0.007*	9.158	1.840	45.579
RTS value(<6.02)	2.345	0.032*	10.435	1.217	89.461
Δ ACR(<130.35)	1.636	0.022*	5.133	1.266	20.809

GCS=Glasgow Coma Scale, RTS=Revised Trauma Score, ACR=Albumin Creatinine Ratio, Δ ACR= difference between ACR1 and ACR2, OR=Odds Ratio, B= Beta Coefficient, CI=Confidence Interval, p-value=.002 is significant.

Discussion

The need to predict the duration of mechanical ventilation (MV) has been recognized as important [23].

It has been stressed that a period longer than seven days of oral or nasal endotracheal intubation significantly increases the risks for laryngotracheal pathology [19,20]. Thus, in this report, seven days of ventilatory support was selected as the cutoff for defining long-lasting assisted ventilation [17,18].

The current study showed highly significant difference between the two groups as regard Revised Trauma Score (RTS) values (p=≤0.001). RTS values were lower in group (B) than group (A). Thus, the more severe the illness as determined by lower RTS values as in group B, the more prolonged mechanical ventilation. This agreed with Arabi *et al.*[24] In addition, Orhon *et al.*[25] stated that all scores[Injury Severity Score (ISS), New Injury Severity Score (NISS), Revised Trauma Score (RTS) and Trauma Score Injury Severity Score (TRISS)] were effective for determining the need for mechanical ventilation (p<0.05). But, when their significance was compared according to their p values it was listed as TRISS, RTS, NISS, and ISS, respectively.

Furthermore, the present study revealed no significant difference between the two groups as regard the amount of fluids delivered to the patients over the first 24 hours of ICU admission (p value >0.05). This was consistent with the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network [26].

In opposition, Alsous *et al.*[27], Boyd *et al.*[28], Correa *et al.*[29], Murphy *et al.*[30] stated that Fluid management was crucial in the treatment of critically ill patients, particularly for those with acute circulatory failure. Accumulating evidence suggests that either hypovolemia or fluid

overload can lead to poor clinical outcomes, including prolonged mechanical ventilation, higher mortality, renal dysfunction and impairment in oxygenation.

Then again, the current study showed no significant difference between the two groups as regard Mean Base Deficit (BD), (p value >0.05). On the contrary, Estenssoro *et al.*[31] concluded that the presence of shock on ICU admission day was the only prognostic factor that predict prolonged mechanical ventilation in the ICU, even adjusting for severity of illness and hypoxemia.

Another interesting finding in the present study was the significant difference between the two groups as regard GCS (p=≤.001). GCS was lower in group B than group A. By using logistic regression analysis for prediction of group (B), GCS <9 was found to be the best significant predictor of MV >7days and GCS<9 accounted for 74.2% of the variance of MV >7days. This was in agreement with Ross *et al.*[32] and Major *et al.*[33] On the other hand, Coplin *et al.*[34] found that a GCS score of ≤ 8 delayed the extubation but did not preclude successful extubation in brain-injured patients.

Interestingly, the current study showed a high incidence of albuminuria on admission. Approximately 62.9% of the patients were microalbuminuric who had ACR level between 30 and 300 mg /g, Similarly, Honarmand *et al.*[13] suggested also a high incidence (70%) of microalbuminuria on the first day of admission and the highest incidence was found on the day of connecting the patients to the mechanical ventilation (78.3%) and Approximately 63% of the patients had ACR level between 30 and 300 mg /g.

The present study showed that there was no significant difference between the two groups as regard ACR1 and ACR2 (p value >0.05) while there was a significant difference between the two groups as regard Δ ACR (p value=0.002). Δ ACR is lower in group B than in group A. by using logistic regression analysis for prediction of prolonged mechanical ventilation in group (B), ΔACR<130.35 was found to be a significant predictor of MV >7days. So, Δ ACR was better in prediction of MV>7 days than ACR1 and ACR2.

Thus, it seemed that the more severe the injury, as implicated from the RTS value, the less the ΔACR and the greater the duration of mechanical ventilation to be expected. Similarly, Basu *et al.*[35], Mackinnon *et al.*[36], Gosling *et al.* [37], and Abid *et al.*[38]found that failure of ACR to decline was associated with increased ICU mortality. While, a decreasing trend of microalbuminuria at 24 hrs of ICU admission may indicate an attenuation of endothelial dysfunction and improvement in organ function, a positive response to the initial therapy [35].

Moreover, Abid *et al.*[38] demonstrated an association between increasing microalbuminuria over the first 48 h and in-hospital mortality, development of acute respiratory failure, and multiple organ failure. Increasing albuminuria had a sensitivity of 60% and a

specificity of 68% in predicting mortality. Respiratory failure, the primary cause necessitating mechanical ventilation, was more common in patients with increased microalbuminuria during the days of hospital admission. It is thus logical that the duration of mechanical ventilation in these patients becomes more prolonged and persistent.

Finally, this table summarizes the studies examined predictors for prolonged mechanical ventilation in trauma patients:

Predictors for prolonged mechanical ventilation

Factors	References	Comments
Older age	(**Dunham *et al.***,1984) [39]	Age> 40 associated with prolonged mechanical ventilation but only in conjunction with other factors.
Low GCS	[(**Dunham *et al.***,1984) [39] , (**Koh *et al.***, 1997) [40] , (**Sustic *et al.***,2002) [41] , (**Velmahos *et al.***,1997) [17] , (**Kollef *et al.***,1999) [42]]	GCS ≤7-8 on admission is highly predictive of prolonged mechanical ventilation. Mean GCS ≤6 on day 3.
Oxygenation	[(**Dunham *et al.***,1984) [39], (**Griffiths *et al.***,2005) [43]]	Measured either as A-a O2 gradient or PaO2/FiO2 ratio, low oxygenation associated with prolonged mechanical ventilation (A-a O2 ≥100 or PaO2/FiO2 ≤250).
Injury Severity Score	[(**Sustic *et al.***,2002) [41], (**Griffiths *et al.***,2005) [43]]	>25 associated with prolonged mechanical ventilation.
Nosocomial pneumonia / witness aspiration	[(**Koh *et al.***, 1997) [40] , (**Stocchetti *et al.***,2000) [44]]	Increased risk of prolonged mechanical ventilation.

Reintubation	(**Stocchetti *et al.***,2000) [44]	Increased risk of prolonged mechanical ventilation by 2.21 times.
Hemodynamic/ fluid balance	[(**Griffiths *et al.***,2005) [43]]	Use of Swan Ganz Catheter and positive fluid balance were associated with prolonged Mechanical ventilation.
SAPS	(**Velmahos *et al.***,1997) [17]	SAPS ≥16 on day 4 of ICU.

Conclusion

Glasgow Coma Score (GCS), Revised Trauma Score (RTS) value and Δ Albumin Creatinine Ratio (Δ ACR) predicted need for and duration of Mechanical Ventilation (MV) >7days.

Failure of microalbuminuria to decline was associated with prolonged mechanical ventilation.

Conflict of interests

None.

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