Correlation of microalbuminuria and outcome in patients with extensive burns†

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Background. Microalbuminuria, often referred to as the urinary albumin–creatinine ratio (ACR), is thought to be a reflection of increased capillary permeability associated with the systemic inflammatory response syndrome, and has been found to be predictive of outcome in several studies. Therefore, we explored the usefulness of ACR as a predictor of mortality, and whether there was a correlation between ACR and \( P_{aO_2}/F_I_{O_2} \) ratios in patients with extensive burns.

Methods. A retrospective observational study was carried out on all patients with extensive burns admitted to the burns intensive care unit. All adult patients with burns of at least 40%, or those with significant inhalational injury, were included. Exclusion criteria were paediatric patients or those with non-thermal processes such as Stevens–Johnson’s syndrome. ACR was measured daily, and data including \( P_{aO_2}/F_I_{O_2} \) ratios were collected. The outcome studied was mortality.

Results. A total of 21 patients were studied, of which there were 7 mortalities. Data were analysed using SPSS Ver11. Patient characteristic data between survivors and mortalities were similar. We did not find any correlation between trends of ACR with \( P_{aO_2}/F_I_{O_2} \) ratios. However, in non-survivors, there were two peaks in ACR, an early peak at days 8–9, and a later peak at day 32, whereas concentrations remained stable in survivors.

Conclusion. We conclude that while ACR is useful as a predictor of mortality and that mean ACR of more than 20 mg mmol\(^{-1}\) is associated with poorer outcome, changes in ACR do not reflect changes in the patients’ immediate clinical conditions.

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Microalbuminuria was initially used to predict the onset of chronic renal failure in diabetic patients. Recently, it has shown promise as an early predictor of disease severity in many acute inflammatory conditions.1 More importantly, it has been found to be predictive of mortality in a heterogeneous group of critically ill patients.2

Microalbuminuria is defined as a urinary albumin concentration of 30–200 mg litre\(^{-1}\). It is generally expressed as the urinary albumin to creatinine ratio (ACR) to correct for variations in urinary flow rate. Calculation of albumin excretion rate requires a timed urinary collection, whereas ACR is calculated from a spot urine test. However, this is based on the assumption that the urinary creatinine excretion rate remains constant.1 The normal value of ACR3 is less than 2.3 mg mmol\(^{-1}\), although it has been found that the prevalence of microalbuminuria in normal healthy adults is up to 3.3%.4 Thus, it has been suggested that higher values be accepted for critically ill patients;5 with some suggesting that a 3-fold increase above the upper normal limit be used as an index of severity of systemic responses.6

In normal healthy kidneys, filtered albumin is reabsorbed after zero-order kinetics which are close to saturation. Therefore, any increase in capillary permeability should result in an increase in microalbuminuria, and hence, it is thought that ACR reflects the glomerular component of systemic microvascular permeability. Although several authors have questioned the view that an increase in systemic permeability is mirrored by a similar increase in

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glomerular permeability, this was confirmed by Shearman and colleagues who showed a correlation between systemic and glomerular permeability using high molecular weight dextran.

In patients with burn injuries, a marked increase in capillary permeability is seen from the immediate onset of burns. It has been reported that an increase in microalbuminuria is seen within an hour of injury. As the use of ACR as a predictor of outcome has not been exclusively studied yet in patients with extensive burns, we designed a pilot study to determine if there was indeed such a correlation.

Methods

Design

A retrospective observational study was conducted on all patients with extensive burns who were admitted to a regional burns intensive care unit over a period of 2 yr. All adult patients with burns of at least 40%, or those with significant inhalational injury requiring intubation and ventilation were included in the study. The percentage burns of 40% was chosen as it represents the point of inflection on the survival curve of burns patients, from which point mortality increases exponentially. Exclusion criteria were paediatric patients and patients with non-thermal processes such as the Stevens–Johnson’s syndrome.

Parameters recorded included patient characteristic data such as age, gender, ASA physical status and weight. ACR was routinely measured and recorded daily. Other data recorded were percentage burns and \( P_{A\over2}/F_{I\over2} \) ratios.

The outcome studied was mortality.

Analysis of urine

A fresh early morning sample of urine was collected daily via indwelling urinary catheters. ACR was measured using the DCA 2000 Analyser from Bayer, which runs a quantitative assay for microalbumin and creatinine in the urine sample. Only 0.4 ml of urine is required for the analysis. The principle of measurement of microalbumin is based on immunoturbidimetry, and that of creatinine based on colorimetry. The albumin to creatinine ratio is then calculated, and the machine gives a result, which is expressed in mg mmol\(^{-1}\) after 7 min.

Statistical methods

The data were analysed using SPSS for Windows Version 11. As it could not be assumed that the data followed a normal distribution, significance was assessed using the non-parametric Mann–Whitney \( U \)-test. Statistical significance was obtained as \( P<0.05 \). Non-parametric correlation was studied using the Spearman’s correlation coefficient.

Results

There were a total of 21 patients studied over the 2-yr period, of which there were 14 survivors and 7 mortalities. No difference in patient characteristic data could be detected between survivors and non-survivors (Table 1).

Two patients amongst the mortalities were classified as ASA II. One of them had ischaemic heart disease and the other suffered from hypothyroidism. All the patients from the survivors were classified as ASA I. The incidence of inhalational injuries was 3 in the survivor group and 2 in the mortality group.

There is a large variation of mean ACR over time in both survivors and non-survivors. However, there appears to be a biphasic variation in the mortality group (Fig. 1). Marked elevation in ACR was observed on days 8 and 9, and a later peak at days 31 and 32. However, in the survivor group, there was no obvious identifiable peak in ACR.

Our data also suggest that percentage mortality increases with mean ACR in a non-linear fashion (Fig. 2), and that mean ACR values of between 15 and 20 mg mmol\(^{-1}\) have mortality of 80%.

We found that although percentage burns tended to be higher in patients who died, this did not reach statistical significance. However, we demonstrated a significant difference in maximum ACR between survivors and non-survivors, with a \( P \)-value of 0.002 (Table 2). There was no difference in admission ACR between the two groups.

Lastly, we plotted the relationship of ACR against \( P_{A\over2}/F_{I\over2} \) ratios for each patient. There was a wide variation in correlation coefficients, with 10 being positive, and 11 being negative. The clear conclusion, based on this set of data, is that there is no consistent correlation between ACR and \( P_{A\over2}/F_{I\over2} \) ratios.

Discussion

In this pilot observational study, we found that mean ACR of 20 mg mmol\(^{-1}\) or more was associated with poorer outcome in patients with extensive burns. There also appeared to be a biphasic variation of mean ACR in patients who died, with either an early peak in the first week of injury, or a later peak a month later. Lastly, the maximum ACR recorded for each patient was significantly higher in the mortality group as compared with those who survived. However, no differences could be found for ACR done on admission.

<table>
<thead>
<tr>
<th>n</th>
<th>Survivors</th>
<th>Non-survivors</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>42.4 (25–58)</td>
<td>45.9 (29–68)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>10:4</td>
<td>4:3</td>
</tr>
<tr>
<td>ASA (I:II)</td>
<td>14:0</td>
<td>5:2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.9 (14.8)</td>
<td>80.0 (19.3)</td>
</tr>
</tbody>
</table>

\( n \), number in each group
Our findings are in keeping with that of several authors. In a study of 50 patients in a heterogeneous ICU population, MacKinnon and colleagues calculated probability of death for ACR and suggested that a rapid indication of outcome can be obtained within 6 h of ICU admission. Similarly, Gosling and colleagues reported that elevated ACR predicted death and APACHE II (acute physiological and chronic health evaluation) scores did. In septic surgical patients, ACR was found to correlate with the sequential organ failure assessment scores. It was also reported that ACR continued to increase in patients who were septic, whereas it remained stable in patients who were not.

The two peaks of ACR observed in our study in the mortality group correlates with the two cascades of multi-organ failure as described by Goodwin in 1990. The early cascade, occurring within the first week, is characterized by failure of reversal of burn shock. The late cascade is typified by an infectious process, and is usually associated with pneumonia.

Most authors advocate that ACR measured on admission to ICU, in particular within 6 h from the initial insult, to be most reflective of disease severity and outcome prediction. However, we could not find a correlation with admission ACR and outcome. This contradicts Gosling’s findings in 2003 where he found that elevated ACR within 15 min of the patients’ admission to ICU correlated with mortality. We speculate that our findings did not correlate with outcome as most of our patients are not admitted directly to the burns unit, but from a referring hospital where they were initially stabilized. Hence, the ACR measured on admission to our ICU is not a true reflection of early ACR elevation.

Traditionally, outcome prediction in burns patients depended on the extent or burns and the presence of underlying medical problems. We found that although the percentage burns tended to be higher in the mortality group, this did not reach statistical significance (P=0.053). We speculate that the reason for this is the relatively small sample size in our study and would expect a significant difference in an adequately powered study.

We could not find a correlation between ACR concentrations and $P_{aO_2}/F_{I_2}$ ratios. This is in keeping with findings by several investigators such as De Gaudio and Szakmany in 2003. Molnar and colleagues could also not demonstrate a correlation between ACR and extravascular lung water.

<table>
<thead>
<tr>
<th>% Burns</th>
<th>ACR-Max (mg mmol$^{-1}$)</th>
<th>ACR-Adm (mg mmol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>52.9 (15.7)</td>
<td>14.0 (15.9)</td>
</tr>
<tr>
<td>Non-survivors</td>
<td>65.7 (23.5)</td>
<td>62.5 (82.1)</td>
</tr>
<tr>
<td>Significance (P)</td>
<td>0.053</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Fig 1 Temporal relationship of average ACR between survivors and non-survivors.

Fig 2 Relationship of mean ACR with mortality.
This could be due to the fact that the causes of decreased $P_{aO_2}/F_{IO_2}$ ratios are multifactorial and not solely due to increased vascular permeability alone.

Therefore, we conclude that in patients with extensive burns, ACR is a useful predictor of mortality, and that ACR of more than 20 mg mmol$^{-1}$ is associated with poorer outcome. However, we acknowledge the limitations of a small retrospective pilot study such as this, and propose that larger prospective trials be carried out to determine if such a correlation does exist.

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