

INVESTIGATING THE RELATIONSHIP BETWEEN MICROALBUMINURIA AND PROGNOSIS OF PATIENTS WITH SEVERE BURNS IN THE MOTAHARI BURN HOSPITAL

ÉTUDE DE LA VALEUR PRONOSTIQUE DE LA MICROALBUMINURIE CHEZ LES PATIENTS BRÛLÉS PRIS EN CHARGE DANS LE CTB DE L'HÔPITAL MOTAHARI

Roham M.,¹ Anbari K.,² Fatemi M.J.,¹ Momeni M.¹✉

¹ Burn Research Center, Iran University of Medical Science, Motahari Burn Hospital, Tehran, Iran

² Health Research Center, Faculty of Medicine, Lorestan University of Medical Science, Khoramabad, Iran

SUMMARY. Microalbuminuria seems to be a reflection of increased vascular permeability caused by systemic inflammatory response, and is likely to be a predictor of mortality, sepsis and other outcomes of severe burn patients. We investigated the impact of microalbuminuria on the prognosis of patients with severe burns. This is a prospective study on severe burn patients (above 20%) admitted in the first 24 hours after burns to the Motahari Burn Hospital. Patients' microalbuminuria was measured at admission and 48 hours later, and its relationship with patient prognosis (sepsis, renal failure, death, inhalation injury and systemic inflammatory response syndrome) was analyzed. We concluded that microalbuminuria at admission in patients with severe burns was directly related to inhalation injury ($P = 0.018$), ARDS during hospitalization ($P = 0.001$) and length of hospital stay ($P = 0.025$). Moreover, microalbuminuria at 48 hours after admission had a direct connection with patient death ($P = 0.001$), sepsis ($P = 0.001$), renal failure ($P = 0.001$) and SIRS ($P = 0.001$). Microalbuminuria is a simple, non-invasive, fast and affordable test to predict sepsis, mortality, renal failure, systemic inflammatory response and a finding associated with inhalation injury in severe burn patients, making it a fast prognostic predictor that helps to improve the management of these patients.

Keywords: burns, prognosis, microalbuminuria, sepsis, inhalation injury

RÉSUMÉ. Une microalbuminurie semble traduire l'augmentation de perméabilité capillaire due à une réaction inflammatoire systémique et pourrait être un paramètre pronostic de mortalité, sepsis et autres évolutions des patients gravement brûlés. Nous avons étudié la relation entre microalbuminurie et devenir des patients sévèrement brûlés. Il s'agit d'une étude conduite chez des patients brûlés sur plus de 20% de SCT admis dans le CTB Motahari dans les 24 h suivant l'accident. La microalbuminurie a été mesurée à l'entrée et à h48 et son association avec une inhalation de fumée ainsi qu'avec le devenir du patient (sepsis, insuffisance rénale, décès, réponse inflammatoire systémique) a été analysée. La microalbuminurie à l'entrée est associée avec l'inhalation de fumées ($p=0,018$), la survenue d'un SDRA ($p=0,001$) et la durée d'hospitalisation ($p=0,025$). La microalbuminurie à h48 est associée au décès ($p= 0,001$), au sepsis ($p= 0,001$), à l'insuffisance rénale ($p= 0,001$) et au SIRS ($p= 0,001$). La microalbuminurie est un marqueur simple, rapide et abordable, fortement corrélé au sepsis, à la mortalité, à l'insuffisance rénale, au SIRS, fréquemment associé à une inhalation de fumées. Ceci en fait un marqueur pronostic rapide pouvant aider à améliorer la prise en charge de ces patients.

Mots-clés: brûlure, pronostic, microalbuminurie, sepsis, inhalation de fumées

Introduction

Severe burns cause endothelial dysfunction and microvascular leakage of proteins and fluid into the interstitial space, which is one of the systemic inflammatory responses. In 1961 Arturson found that burn animal models with TBSA (Total Body Surface Area) more than 30% experience systemic vascular leakage in the first 24 hours.¹ Even the departure of protein increased 100 times in damaged tissues and up to 5 times in healthy tissues.²

Microalbuminuria was first used for monitoring diabetic

nephropathy; however nowadays it helps as a marker of systemic and local inflammation.³⁻⁵ It seems that it can also be used as a prognostic predictor of different clinical conditions.⁶⁻¹⁰

Albuminuria refers to the high concentration of 200 milligrams per litre of urine and microalbuminuria (MAU) is the pathological secretion of 30-200 mg per litre of albumin with normal molecular weight in urine.¹¹

Microalbuminuria happens following acute inflammations such as in surgery, which gives rise to this hypothesis that microalbuminuria is a reflection of systemic vascular endothelial dysfunction.^{3,12-13} Since then microalbuminuria has been iden-

✉Corresponding author: Mahnoush Momeni, Burn Research Center, Motahari Hospital, Rashid Yasami St, Vali-e-asr Ave, Tehran, Iran. Tel: +98 21 88884275; email: mah_momeni@yahoo.com

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tified as a decisive marker in determining systemic inflammatory response as well as a predictor for prognosis in multiple trauma, major surgery, pancreatitis, meningitis, anaphylaxis and critical diseases.^{4,8,9-10,12,14-15}

In a study conducted in 2011 on patients with acute myocardial infarction, Apostolovic et al.¹⁶ found that microalbuminuria during the first week after admission showed a statistically significant difference ($P < 0.05$) between the two groups, those who survived and those who died in hospital, and within 6 months after infarction. Microalbuminuria was higher in patients who died.

In a study conducted on pediatric burns, Din et al.¹⁷ came to the conclusion that there is a direct connection between the ACR test (albumin/creatinine ratio) and length of stay in the ICU, and also severity of burn and the number of organs that need care.

In a study on burn patients by Cochrane et al.,¹⁸ it was concluded that there was no relationship between ACR (albumin/creatinine ratio) and severe burns and resuscitation, but a connection with blood lactate levels was found. In this study, all inhalation injured patients had microalbuminuria.

Various pro-inflammatory cytokines are involved in the pathogenesis of systemic inflammatory response syndrome (SIRS) that can also be used as an inflammatory marker in laboratory studies of burn patients. These markers are Tumor Necrosis Factor α (TNF α), Interleukin 6 (IL6) and Interleukin 1 (IL1).¹⁹

IL6 is one of the markers that indicate poor prognosis in burn patients. It induces the production of CRP in the liver. CRP along with IL6 is used as a marker for predicting patient mortality.²⁰

In this study we used microalbuminuria as a prognostic marker for severe burn patients.

Materials and methods

This study was conducted on hospitalized patients in the Motahari Burn Hospital from April 2016 (April 1395) to December 2016 (December 1395). The project was reviewed and accepted by the Ethics Committee of Iran University of Medical Sciences.

We studied patients with 20% to 70% burns of both sexes, aged over 16 years who were hospitalized in the intensive care unit, and excluded those with TBSA of more than 70% because it is possible that different variables and parameters cause false positive biased results. According to the American Burn Association criteria, burns more than 20% are considered to be severe burns therefore we chose TBSA of over 20% in our study.²¹

Exclusion criteria involved patients admitted more than 24 hours after burn injury or who had underlying diseases which affected their kidney function (such as hypertension, diabetes and systemic lupus erythematosus) as well as pregnant women (due to changes in hemodynamics after pregnancy).

We took a complete history of all the patients and they all underwent a physical examination. TBSA was estimated according to the Lund and Browder chart.

All patients were resuscitated on the first day of admission to restore diuresis (urine), 30 to 50 ml per hour. Antibiotics were not given routinely and if signs of infection were observed (based on clinical symptoms and positive blood culture and swab culture) they were given antibiotics based on an an-

tibiogram. Wound care and dressing based on the protocol were checked daily. Surgical treatments such as escharotomy or excision and autograft were carried out when necessary.

Clinical diagnosis of SIRS or Systemic Inflammatory Response was based on at least two of the following parameters:²²

- Body temperature above 38 or below 36.
- Heart rate above 90 beats per minute.
- Respiratory rate of 20 per minute or less than 32 mm Hg PCo₂.
- WBC more than 12,000 or less than 4000 or Bandemia above 10%.

CBC, electrolytes, liver and kidney function tests and serum albumin were performed daily for all patients. One urine sample at admission and another one 48 hours later was sent to the laboratory to evaluate microalbuminuria. Whenever necessary, wound and blood cultures were obtained from patients. Microalbuminuria was measured by Naycocard kit and immunoassay method (made in Norway).

According to the American Burn Association Consensus Conference, sepsis diagnosis was obligatory for all patients.²³

Patients whose urine albumin was between 30 to 200 mg per litre were considered to be patients with microalbuminuria.

The sample size in terms of the prevalence of 10% and 20% difference in the two groups of survival with regard to alpha error = 0.5 and beta error = 0.2 based on software G * Power 3.1.3 was about 62 people. Chi-square, T test and Pearson correlation coefficient tests were used.

Results

The number of patients during the 10-month study was 62. Frequency of women and men was respectively 45 (72.6%) and 17 (27.4%), and male to female ratio was 17:54. The mean age of patients was 35.53 ± 11.73 : the youngest patient was 16 and the oldest 75 years old. The average duration of stay in the ICU and hospital was 10.01 ± 8.06 and 16.2 ± 9.9 days respectively.

Forty patients (64.5%) were discharged and 22 (35.5%) died. Sepsis occurred in 18 (29%). Inhalation injury was positive in 23 cases (37.1%) and negative in 39 cases (62.9%). Acute renal failure was positive in 19 cases (30.6%) and negative in 43 cases (69.4%). SIRS was positive in 36 cases (58.1%) and negative in 26 cases (41.9%).

ARDS or Adult Respiratory Distress Syndrome was positive in 13 cases (21%) and negative in 49 cases (79%). Pneumonia was diagnosed in 13 patients (21%) but not in the other 49 cases (79%). Microalbuminuria at admission was positive in 31 patients (50%) and negative in 31 (50%). This was the same 48 hours after admission. TBSA (Total Body Surface Area) was 52.85 ± 18.07 in patients. The mean of microalbuminuria in patients at and 48 hours after admission is shown in *Table I*.

Table I - Mean and standard deviation of microalbuminuria in patients at and 48 hours after admission

| Time | Mean \pm SD | Range |
|--------------------|------------------|---------|
| At admission | 48.01 \pm 52 | 3 – 200 |
| 48h post admission | 58.19 \pm 58.9 | 5 – 200 |

Table II - Contingency table of distribution of sepsis incidence, inhalation injury, renal failure and systemic inflammatory response in patients with and without microalbuminuria divided by length of hospital stay

| Time | Sepsis | | Inhalation injury | | Renal failure | | SIRS | |
|-------------------------------|--------------|-------------|-------------------|-------------|---------------|-------------|--------------|-------------|
| | Yes N (%) | No N (%) | Yes N (%) | No N (%) | Yes N (%) | No N (%) | Yes N (%) | No N (%) |
| MAU at admission | | | | | | | | |
| Yes N (%) | 9 (29) | 22 (71) | 16 (51.6) | 15 (48.4) | 10 (32.3) | 21 (67.7) | 21 (67.7) | 10 (32.2) |
| No N (%) | 9 (29) | 22 (71) | 7 (22.6) | 24 (77.4) | 9 (29) | 22 (71) | 15 (48.4) | 16 (51.6) |
| P-value | 0.999 | | 0.018 | | 0.783 | | 0.123 | |
| MAU 48h post admission | | | | | | | | |
| Yes N (%) | 17 (54.8) | 14 (45.2) | 9 (29) | 22 (71) | 19 (61.3) | 12 (38.7) | 25 (80.6) | 6 (19.4) |
| No N (%) | 1 (3.2) | 30 (96.8) | 14 (4.2) | 17 (54.8) | 0 (0) | 31 (100) | 11 (35.5) | 20 (64.5) |
| P-value | <0.001 | | 0.189 | | 0.001 | | <0.001 | |

Table III - Contingency table of frequency distribution of ARDS, pneumonia and death in patients with and without microalbuminuria divided by length of hospital stay

| Time | ARDS | | Pneumonia | | Death | |
|-------------------------------|--------------|-------------|--------------|-------------|--------------|-------------|
| | Yes N (%) | No N (%) | Yes N (%) | No N (%) | Yes N (%) | No N (%) |
| MAU at admission | | | | | | |
| Yes N (%) | 12 (38.7) | 19 (61.3) | 7 (22.6) | 24 (77.4) | 13 (41.9) | 18 (58.1) |
| No N (%) | 1 (3.2) | 30 (96.8) | 6 (19.4) | 25 (80.6) | 9 (29) | 22 (71) |
| P-value | 0.001 | | 0.557 | | 0.288 | |
| MAU 48h post admission | | | | | | |
| Yes N (%) | 6 (19.4) | 25 (80.6) | 12 (38.7) | 19 (61.3) | 22 (71) | 9 (29) |
| No N (%) | 7 (22.6) | 24 (77.4) | 1 (3.2) | 30 (96.8) | 0 (0) | 31 (100) |
| P-value | 0.775 | | 0.001 | | <0.001 | |

There was no direct linear relationship between microalbuminuria at admission and age (P value=0.236) and also burn percentage (P value=0.377). There was a direct linear relationship between microalbuminuria 48 hours after admission and burn percentage (P value<0.001).

However, there was no direct linear relationship between microalbuminuria at admission and 48 hours later and hospital stay (p value = 0.025). This means that the incidence of microalbuminuria at admission and 48 hours later increases the length of hospital stay.

There was no direct relationship between microalbuminuria 48 hours after admission and age and length of stay in the ICU.

Based on the results shown in *Table II*, inhalation injury in patients who had microalbuminuria at admission was significantly higher than in those who did not have microalbuminuria (*Table II*). Therefore we found a statistically significant relationship between microalbuminuria at admission and risk of inhalation injury (P = 0.018).

In our study, no significant relationship between microalbuminuria at admission and sepsis, renal failure (P = 0.783) or SIRS (P = 0.123) was observed.

We found a significant statistical relationship between mi-

croalbuminuria 48 hours after admission and sepsis (P<0.001), renal failure (P<0.001) and also SIRS (P<0.001), as based on the chi-square test. Each of these outcomes in patients with microalbuminuria was significantly higher than in those who did not have microalbuminuria.

A significant relationship between microalbuminuria 48 hours after admission and inhalation injury (P = 0.189) was observed.

Based on the results presented in *Table III* respiratory failure syndrome in adults and in patients with microalbuminuria at admission was significantly higher than in those who did not have microalbuminuria. Therefore, we found a significant statistical relationship between microalbuminuria at admission and adult respiratory failure syndrome (P = 0.001).

A significant relationship was not found between microalbuminuria at admission and pneumonia (p = 0.755) and also death (P = 0.288).

We observed a meaningful statistical relationship between microalbuminuria 48 hours after admission and pneumonia (P = 0.001) and death (P <0.001), as the chi-square test proved each of these outcomes in patients with microalbuminuria 48 hours after hospitalization were significantly higher than in those who did not have microalbuminuria. However, there was

no significant relationship between microalbuminuria 48 hours after admission and acute respiratory failure ($P = 0.775$).

According to the independent t-test, the average size of burn was significantly greater in patients with microalbuminuria 48 hours after admission than in those without microalbuminuria ($p = 0.005$).

According to the independent t-test, there was no significant difference in the average size of burn in cases with microalbuminuria at the time of admission and in those without microalbuminuria ($p = 0.376$).

According to the independent t-test, mean age of patients with microalbuminuria 48 hours after admission and those without microalbuminuria was not significantly different ($p = 0.259$).

Based on the independent t-test, mean age of patients with microalbuminuria at admission and those without microalbuminuria was not significantly different ($p = 0.128$).

Discussion

In this prospective study we attempted to find a reliable, fast, simple and affordable prognostic factor in patients with severe burns. After examining several studies, we concluded that microalbuminuria was used as a prognostic factor in some patients, but there have not been a lot of studies on burn patients.

It is very important to determine the prognosis of patients in intensive care units and help make plans for aggressive procedures, consulting with the patient's caregivers and resource allocation. The Acute Physiology, Chronic Health Evaluation (APACHE) and Simplified Acute Physiology Score (SAP score) determine the prognosis of patients who will be admitted to the General ICU,^{24,25} and are not only allocated to burns. Moreover, a prognostic factor used in the ICU should be a short-term factor to show the effects of the treatment measures sooner, as well as have high sensitivity, and should be inexpensive, affordable and dynamic, giving fast and reliable responses.

Critical diseases are mostly diagnosed with systemic inflammatory response (SIRS), which in fact is a host response to acute events in the body that can lead to organ failure and finally death.²⁶

Severe and persistent inflammatory response can cause changes in endothelial function that lead to the destruction of barrier integrity and cause systemic leakage.^{27,28}

It also happens in the kidneys where glomerular permeability and excretion of albumin in urine increases.¹³ Microalbuminuria is seen in conditions such as burns, pancreatitis, meningitis, cerebral ischemia and acute myocardial infarction.^{6,29,30,4,31,32}

An increased level of microalbuminuria in patients is related to multiple organ dysfunctions including serum creatinine, duration of mechanical ventilation, need for vasopressor, physiological scoring system and the ratio of Po_2 / Fio_2 .^{33,15,34,35}

It seems that microalbuminuria can be a predictor of prognosis in patients with different clinical conditions.⁶⁻¹⁰ Rapid prognosis and the adoption of an appropriate protocol can affect treatment interventions, prescription of antibiotics, inotropics and vasopressor use in the early hours of admission to the ICU, and therefore improve endothelial function and increase the patient's chance of survival.³⁶

We estimated that microalbuminuria at admission and 48

hours later can be a reflection of endothelial dysfunction after burn, and indicates the burn patient's prognosis. In previous studies it was found that microalbuminuria occurred in cases such as ischemic lesions, pancreatitis, SIRS, sepsis and metabolic syndromes, as well as transient microalbuminuria in cases such as surgeries.³⁷

In addition, microalbuminuria is a quick indicator to determine ARDS, sepsis and mortality in critically ill patients.¹⁵ In this study we examined the relationship between microalbuminuria at admission and 48 hours later in burn patients with sepsis, acute renal failure, and inhalation injury and mortality, length of hospital stay and SIRS. Based on our results, microalbuminuria is relevant to outcome in these patients.

Although these results may not be generalizable to all burn patients, they appear to have the highest value in adult patients with severe burns.

In a study conducted by Sherif et al., 72.3% of adult patients with severe burns had microalbuminuria,³⁸ which was higher than in our study. This could be due to repeated measurements of urine albumin until discharge or death, while in our study microalbuminuria was only checked twice.

In our study, 37.1% and 21% of the patients had inhalation injury and ARDS, respectively. 69.5% of patients with inhalation injury had microalbuminuria at the time of admission and also during hospitalization. 12 patients out of 13 who were suffering from ARDS had microalbuminuria (92.3%). We also found that microalbuminuria at admission was directly related to inhalation injury and ARDS, and the prevalence of microalbuminuria at the time of admission in these patients was significantly higher ($p = 0.018$ for inhalation injury and $p = 0.001$ for ARDS), but the incidence of these complications had no significant relationship with microalbuminuria 48 hours after admission.

In a study conducted by Sherif³⁸ and another by Cochran,¹⁸ microalbuminuria was seen respectively in 100% and 30% of patients with inhalation injury at the time of admission.

Based on our findings and other studies, microalbuminuria can be used as an indicator for diagnosing inhalation injury at admission. We also suggest adding this test to other diagnostic tests in patients with severe burns.

In another study conducted by Pallister et al., it was reported that microalbuminuria measurement 8 hours after major trauma can be used as a predictor of ARDS, with a positive predictive value of 85%.⁹

In our study 58.1% of patients had SIRS at least once during hospitalization, and 80.6% of them had microalbuminuria after 48 hours. The incidence of SIRS in cases with albuminuria 48 hours after admission was significantly higher than in those without microalbuminuria ($P=0.001$). However, this relationship was not found in cases with microalbuminuria at the time of admission.

In the study by Sherif et al.,³⁸ 83.7% of patients were SIRS-positive and 88.4% of SIRS patients had microalbuminuria.

Comparing our study with others and according to our results, it can be said that SIRS is a common finding in burns above 20%. Since microalbuminuria has a direct relationship with SIRS 48 hours after admission, it should be measured in patients with severe burns and considered alongside other SIRS criteria.

Sepsis occurred in 29% of patients in our study, and in 54.8% of those with microalbuminuria 48 hours after admis-

sion. There was a significant difference with the group without microalbuminuria after 48 hours of admission ($P < 0.001$), but no statistically significant relationship was seen with microalbuminuria at the time of admission.

In the study by Sherif et al. on patients with wound sepsis, 95.1% of them had microalbuminuria.³⁸ Although higher than in our study, the results of both studies indicated that microalbuminuria in patients who may get sepsis during hospitalization was significantly greater.

In previous studies carried out on surgical patients, it was found that the ACR in septic patients remained high for a long time and was associated with body filler.³⁹

In our study, twenty-two patients (35.5%) died: 12 of them had microalbuminuria 48 hours after admission. The prevalence of microalbuminuria in patients who died and those who survived was significantly different ($p < 0.001$).

Yew's study reported that the maximum ACR in patients who died was significantly higher than in those who survived ($P = 0.002$), but there was no significant relationship with patient mortality at the time of admission.³²

In our study, there was no significant relationship between microalbuminuria during admission and mortality ($P = 0.288$), but the mortality of patients with microalbuminuria 48 hours after admission had a significant connection.

In the study by Sherif et al.,³⁸ 2 patients died (4.08%), but mortality rate in our study was 35.53%. One of the reasons for higher mortality in our patients was higher mean age and TBSA (52.8%) compared with the previous study: in Sherif's study children of the same age group and also patients with 20% to 50% TBSA were studied while in our study only adults were enrolled and cases with 20% to 70% burns were examined. It is obvious that older age and higher burn percentage are two important factors in the increase in mortality rate.

In a study conducted on patients admitted to the ICU, Basu et al.⁴⁰ concluded that albumin/creatinine ratio (ACR) in the 24 hours after hospitalization was higher in patients who died, and showed a significant difference with the group that survived ($P < 0.0001$). Although this ratio in those who died was higher at the time of admission, the difference was not statistically significant ($P = 0.0948$). They found that the absence of microalbuminuria in the 24 hours after admission can be a predictor of survival in the ICU.

In the study carried out by Thorevska et al.,³⁴ they found that patients with high albumin/creatinine ratio of 100mg / g at the time of ICU admission are 2.7 times more likely to die than patients in whom this ratio is lower. It was suggested in this study that the microalbuminuria test can be used as a predictor of length of hospital stay, because patients with more ACR and $p = 0.0007$ experienced a longer hospital stay.

In 2006, Gosling et al.³⁵ conducted a study on patients admitted to the ICU. They examined ACR 4-6 hours after admission and concluded that patients who died in the ICU had higher ACR after 4-6 hours and at the time of admission than those who survived (on admission, $p < 0.0002$ and 4 hours after, $p < 0.0001$). Also the duration of treatment for patients with high ACR was longer.

In our study, patients with microalbuminuria at and 48

hours after admission had a longer hospital stay and the difference was statistically significant ($P = 0.025$). Also, microalbuminuria 48 hours after admission had a direct relationship with acute renal failure and a significant difference was seen in the case of renal failure in two groups with microalbuminuria and without microalbuminuria ($P = 0.001$).

In a study undertaken by Alaa et al.⁴¹ on patients with acute renal failure, they found that microalbuminuria increased on the first day and during hospitalization and then reached its peak in the third week compared to those who did not have renal failure.

In our study, 30.6% of cases had acute renal failure, which in the study by Alaa et al. occurred in 22.5% of moderate and severe burn patients. However, compared to our patients it was lower.

In our study the incidence of sepsis had a direct relationship with microalbuminuria 48 hours after hospitalization and a statistical difference between groups with and without microalbuminuria was significant ($P = 0.001$).

In their study conducted on patients admitted to the ICU, Basu et al.⁴² came to the conclusion that ACR in patients who had sepsis was higher than in those without sepsis ($P = 0.0016$) and showed that ACR with 80% sensitivity could distinguish between patients with and without sepsis.

We also concluded that ACR 24 hours after admission, with a sensitivity of 85%, could distinguish between those who survived and those who died. Eventually it was concluded that mortality rate would be lower if patients did not have microalbuminuria within 24 hours of admission to the ICU.

Limitations

We did not examine the impact of medications on microalbuminuria. This is because according to previous studies some drugs and substances increase microalbuminuria.¹¹ Also, antibiotics can cause nephrotoxicity; therefore it is better to investigate their effect.

We did not study patients' BMI because BMI is an effective factor on microalbuminuria.⁴³ It was better if we examined creatinine and also used ACR in data interpretation.

In general, our study was a prospective study that investigated the relationship between microalbuminuria and sepsis, inhalation injury, mortality, incidence of kidney failure and SIRS.

Although previous studies had examined the relationship between microalbuminuria and factors mentioned above, none of them had reviewed all of them together and at the same time.

Recommendations

Microalbuminuria is a simple, fast, non-invasive and cost-effective test that can be used to predict sepsis, ARDS, acute renal failure, mortality and inhalation injury.

Sampling can be carried out each time with urine void or with urinary catheter insertion. This may affect our management of severe burn patients. This test can be a confirmatory test in the incidence of sepsis, renal failure, inhalation injury, ARDS and SIRS.

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