Accompanying mild hypothermia significantly improved the prognosis of septic mice than artificial mild hypothermia

Qilian Xie
Department of Emergency
Anhui Provincial Children's Hospital

昵图网 www.nipic.com BY.linyong
NO:20110216203841537148

Accompanying mild hypothermia significantly improved the prognosis of septic mice than artificial mild hypothermia

Qilian Xie
Department of Emergency
Anhui Provincial Children's Hospital

Background

- Hypothermia, a protective treatment method for acute brain damage that has been considered as the only effective method in the 20th century, has now been popularly accepted in clinical practices
- Interestingly, Some patients with sepsis are found with accompanying mild hypothermia (ACMH);
- however, the effects of ACMH on the patients with sepsis are poorly understood.

Objective

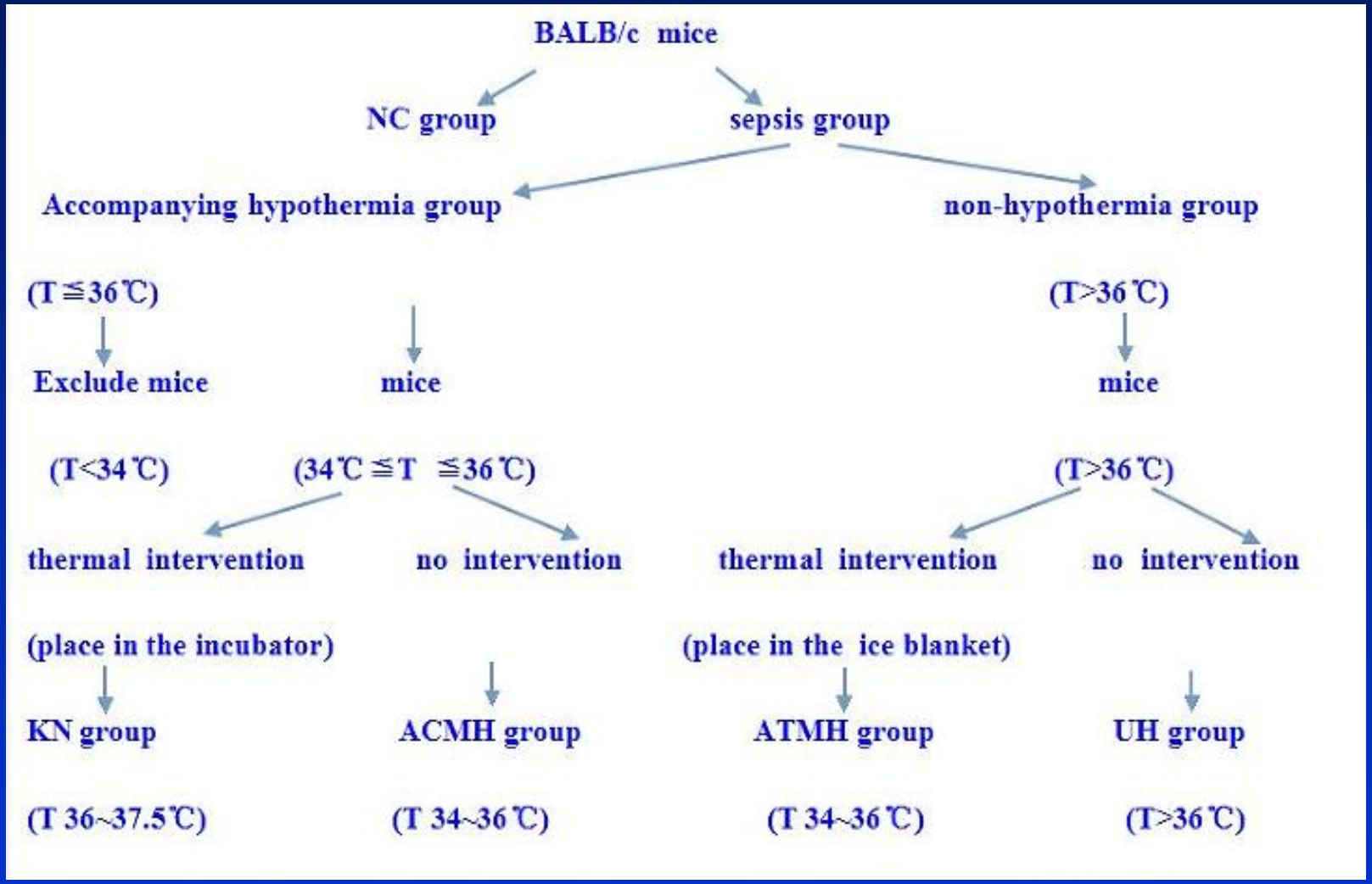
To compare the impacts of ACMH and artificial mild hypothermia (ATMH) on mortality, systemic inflammatory reactions, and organ functions in mice with sepsis.

Methods

Septic mouse models were induced and divided into ACMH, un-hypothermia, keep normothermia, and ATMH groups.According to the anal temperature and the thermic intervention strategy. The mortality rate, serum levels of tumor necrosis factor α (TNF-α), interferon γ(IFN-γ), and interleukin (IL)-4 and liver and renal functions of the mice in each group were recorded.

Liver, lung, and renal tissues of the mice were stained and examined under optic microscope.

Methods



NC group:normal control group. KN group:keep normothermia group. ACMH group: accompanying mild hypothermia group. ATMH group:artificial mild hypothermia group. UH group:un-hypothermia group. T:anal temperature

Results

The mortality rate in the ACMH group was the lowest among all the sepsis groups.

Increased serum levels of TNF-α, IFN-γ, and IL-4 and impairments of the liver and renal functions were found in the septic mice. The serum levels of TNF-α, IFN-γ, and IL-4 were significantly lower and the liver and renal functions of ACMH group were not impaired significantly as compared with other sepsis groups.

Pathological examinations of the lung, liver, and renal tissues showed that the ACMH group were with the lowest pathological score among all the sepsis groups.

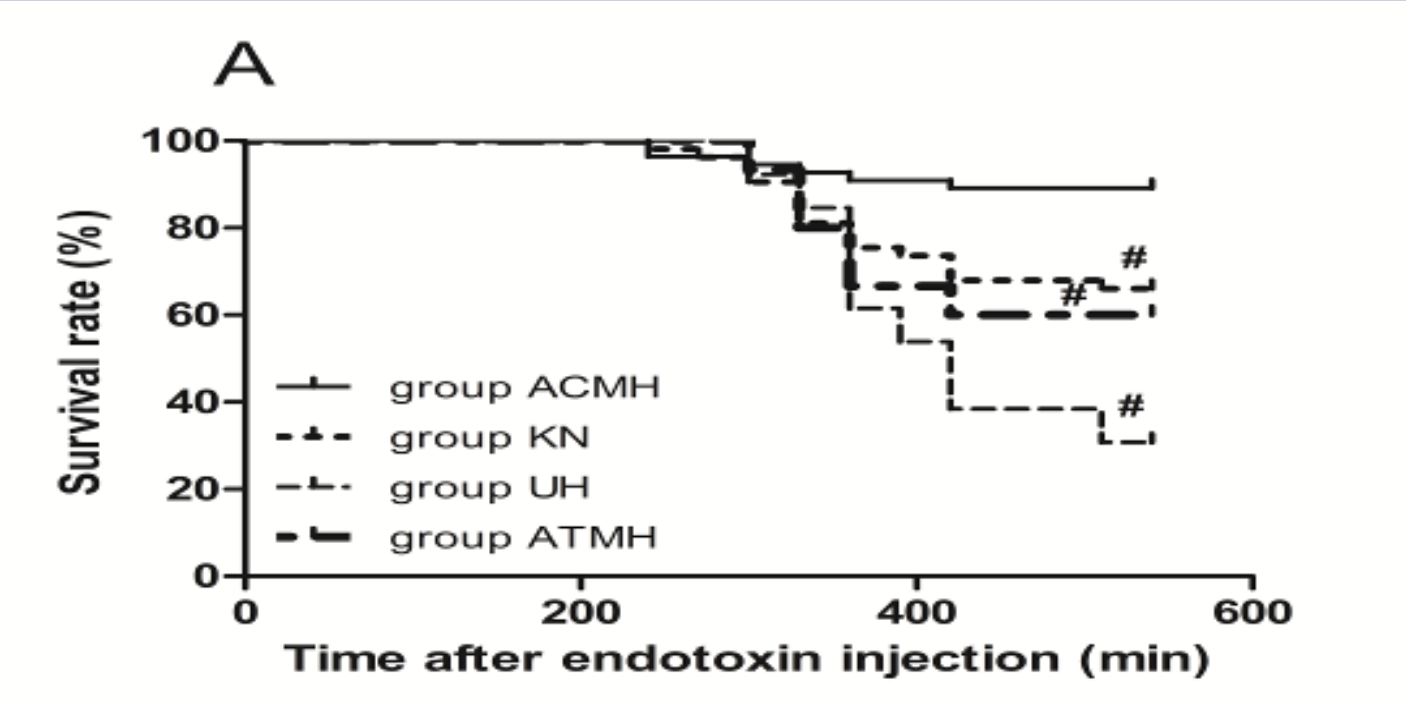
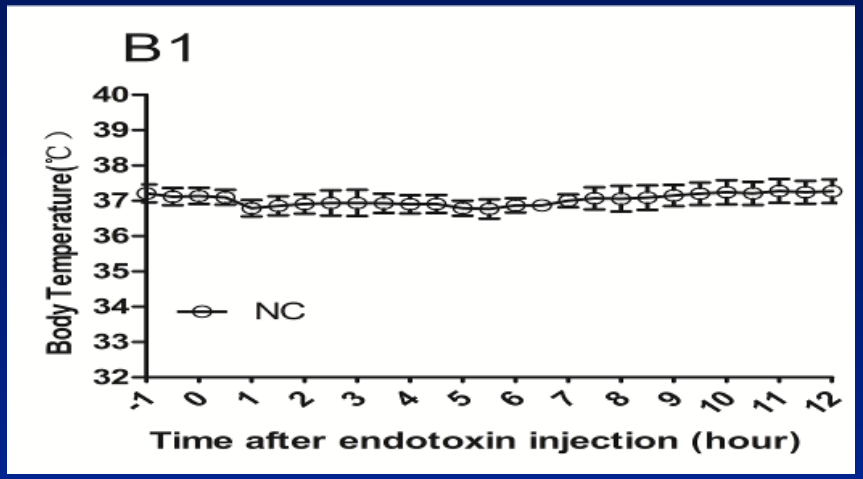
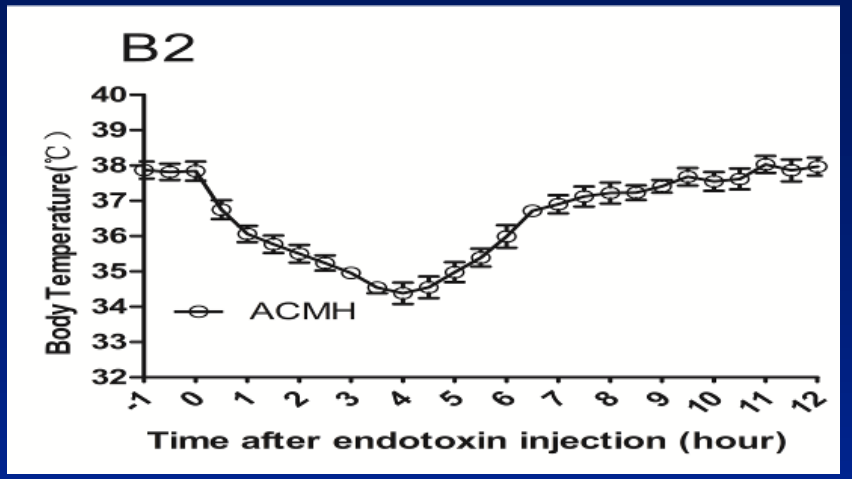
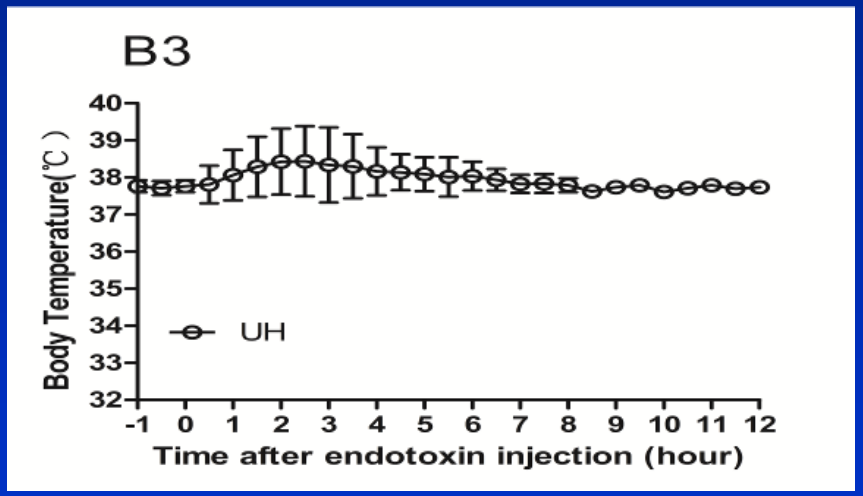


Figure 1 A: Survival rate of the mice. Significant difference in the survival rate was found between the ACMH group and other sepsis groups (#, $P<0.01$), while no significant difference was found between the UH group and the ATMH group ($P>0.05$);







B: the anal temperature of the mice in the NC group maintained between 36.0° C and 37.5° C; the anal temperature of the mice in the ACMH group was basically between 34° C and 36.5° C at 1-6 h after the LPS injection, while the anal temperature of the mice in the UH group was generally between 36.8° C and 39.9° C.

Table 1 Changes of the serum IFN-γ level in the mice

Group	Changes of IFN-γ level with time (pg/ml)		
	6h	12h	24h
NC	215.33±31.22	210.17±17.44	221.33±16.91
ACMH	310.83±69.10#	229.00±46.56	213.17±24.71
KN	416.17±44.87#☆	251.83±66.99	206.50±25.37
UH	452.00±71.15#☆	274.17±52.83*	209.33±33.90
ATMH	372.50±56.78#	216.50±37.39	227.17±24.08

*P <0.05, # P<0.01, comparing with the NC group;
☆P<0.01, comparing with the ACMH group

Table 2 Changes of the serum TNF-α level in the mice

Group	Changes of TNF-α level with time (pg/ml)		
	6h	12h	24h
NC	121.67±20.45	132.17±18.19	127.33±23.86
ACMH	187.50±51.3*	148.50±26.74	124.00±24.55
KN	262.17±75.40#△	179.67±32.26*	129.17±24.08
UH	288.00±65.39#☆	194.50±39.94#△	140.17±32.52
ATMH	252.00±37.88#△	161.83±33.64	121.67±29.73

**P* <0.05, # P<0.01, comparing with the NC group; △P <0.05, ☆P<0.01, comparing with the ACMH group

Table 3 Changes of the serum IL-4 level in the mice

Group	Changes of IL-4 level with time (pg/ml)		
	6h	12h	24h
NC	392.33±37.67	380.50±54.29	404.50±48.92
ACMH	458.50±48.62*	517.00±73.90#	367.00±60.41
KN	470.67±54.28*	536.50±74.30#	398.83±66.43
UH	537.00±66.04#△	628.83±86.97#△	440.50±83.88
ATMH	511.00±59.27#	580.00±82.58#	421.00±74.03

*P<0.05，# P<0.01, comparing with the NC group;
△P <0.05, comparing with the ACMH group

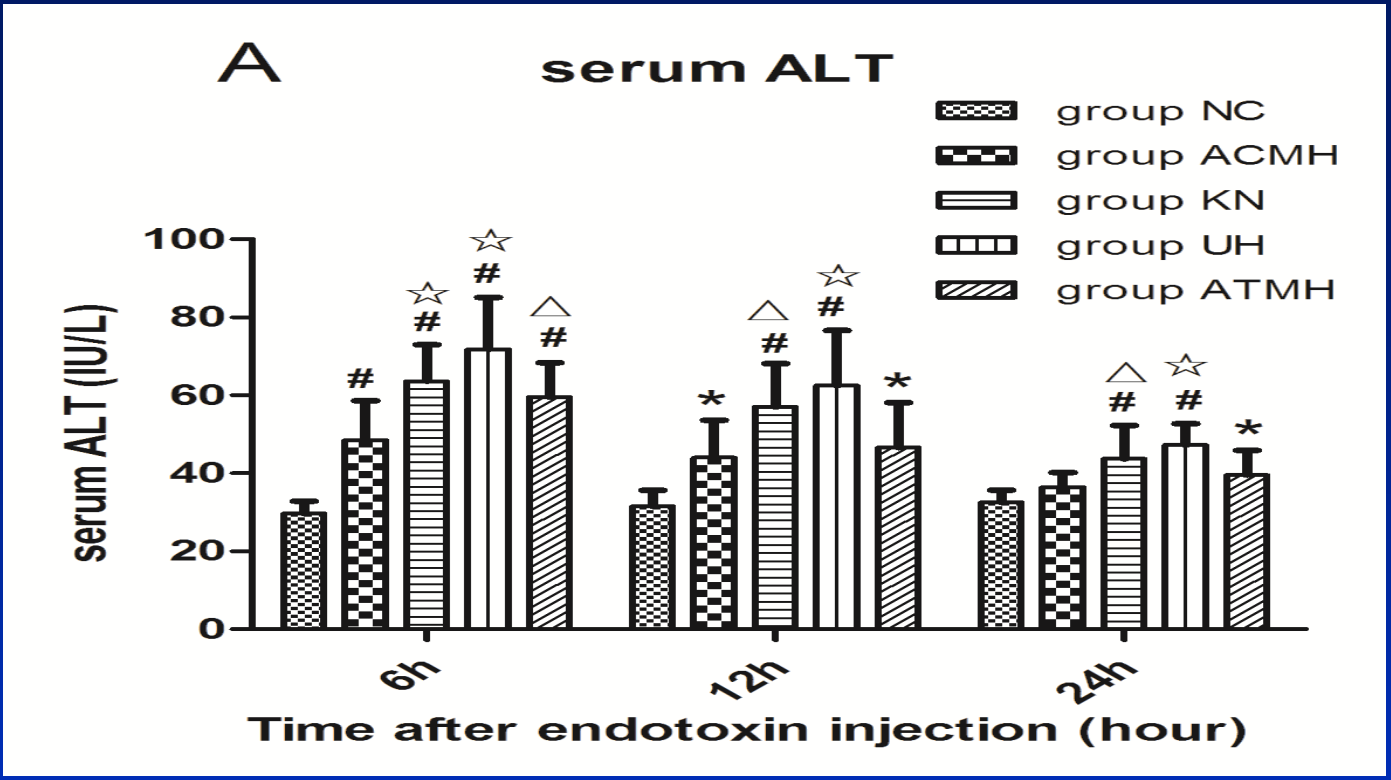
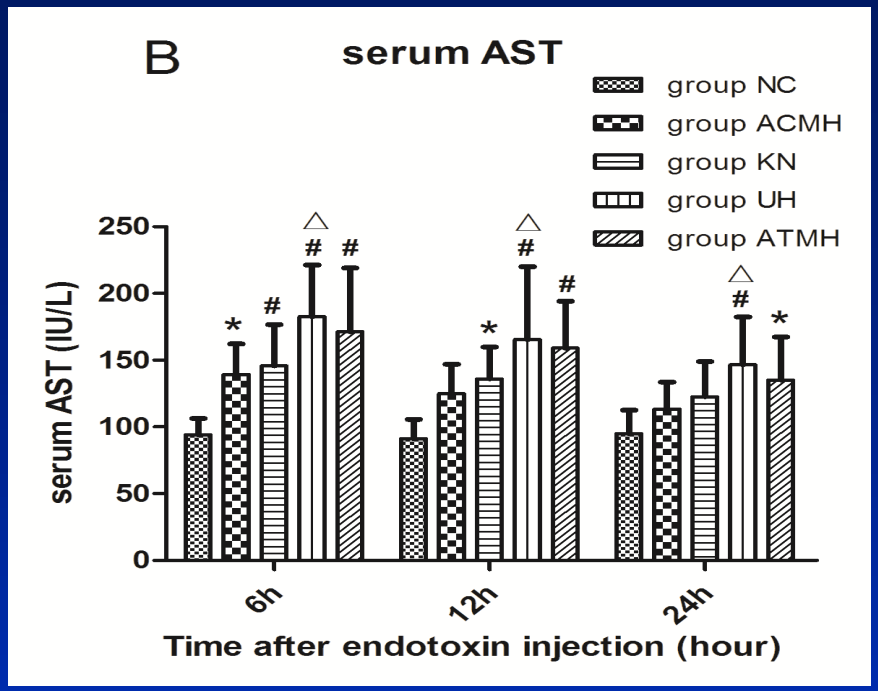


Fig. 2 Comparison between the sepsis groups and NC group (*$P < .05$, #$P < .01$); comparison between the sepsis groups and the ACMH group (△$P < .05$, ☆$P < .01$). A, Significant difference was found in the serum ALT between the ATMH group and the UH group ($P < .05$).



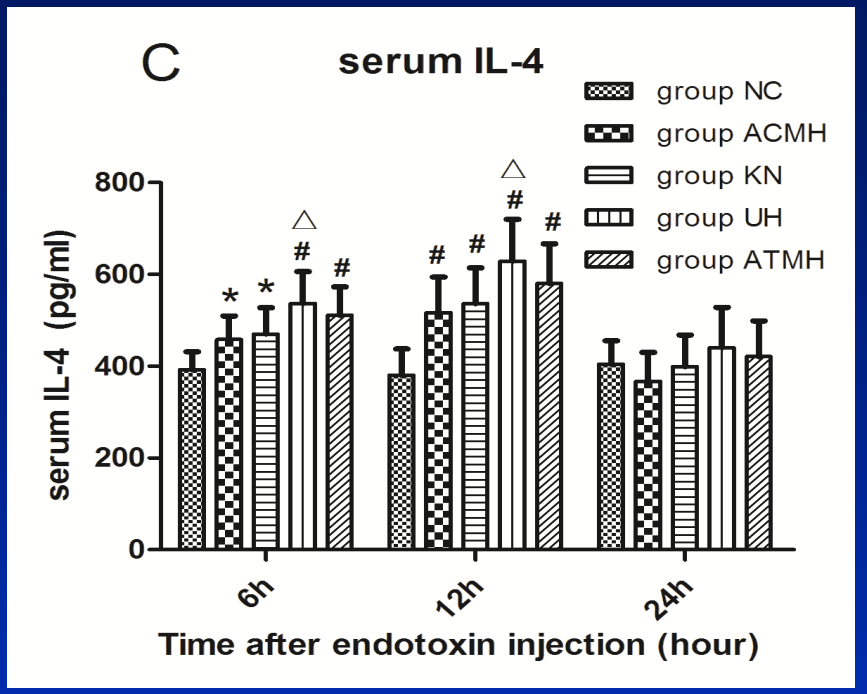
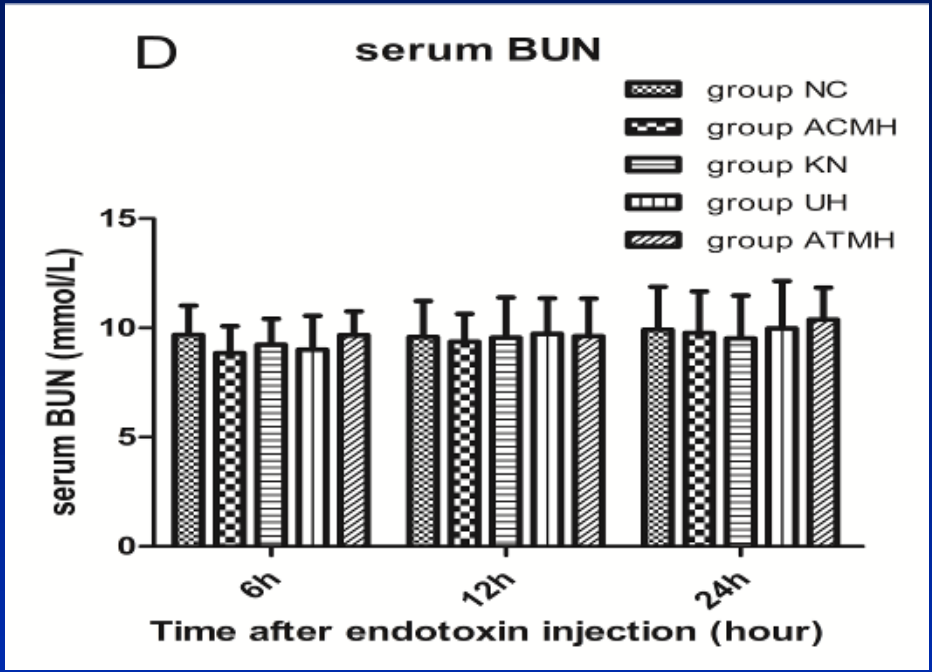


Fig. 2 Comparison between the sepsis groups and NC group (**P* < .05, #*P* < .01); comparison between the sepsis groups and the ACMH group (△*P* < .05, ☆*P* < .01). B and C, No significant difference was found in the serum AST and IL-4 levels between the ATMH group and the UH group (*P* > .05).



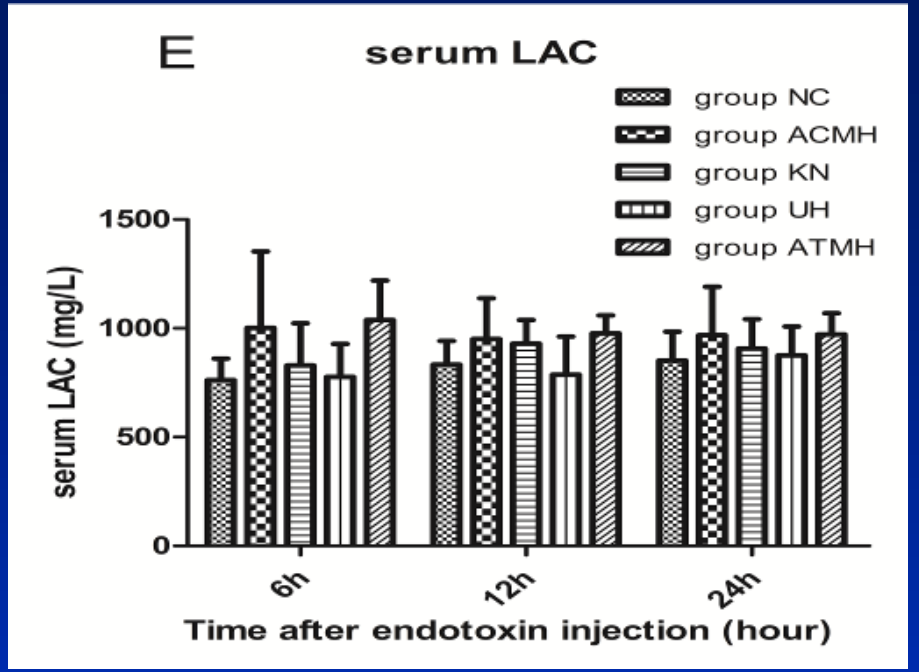


Fig. 2 Comparison between the sepsis groups and NC group (*$P < .05$, #$P < .01$); comparison between the sepsis groups and the ACMH group (△$P < .05$, ☆$P < .01$). D and E, No significant difference was found in the serum BUN and lactate levels among the different groups ($P > .05$).

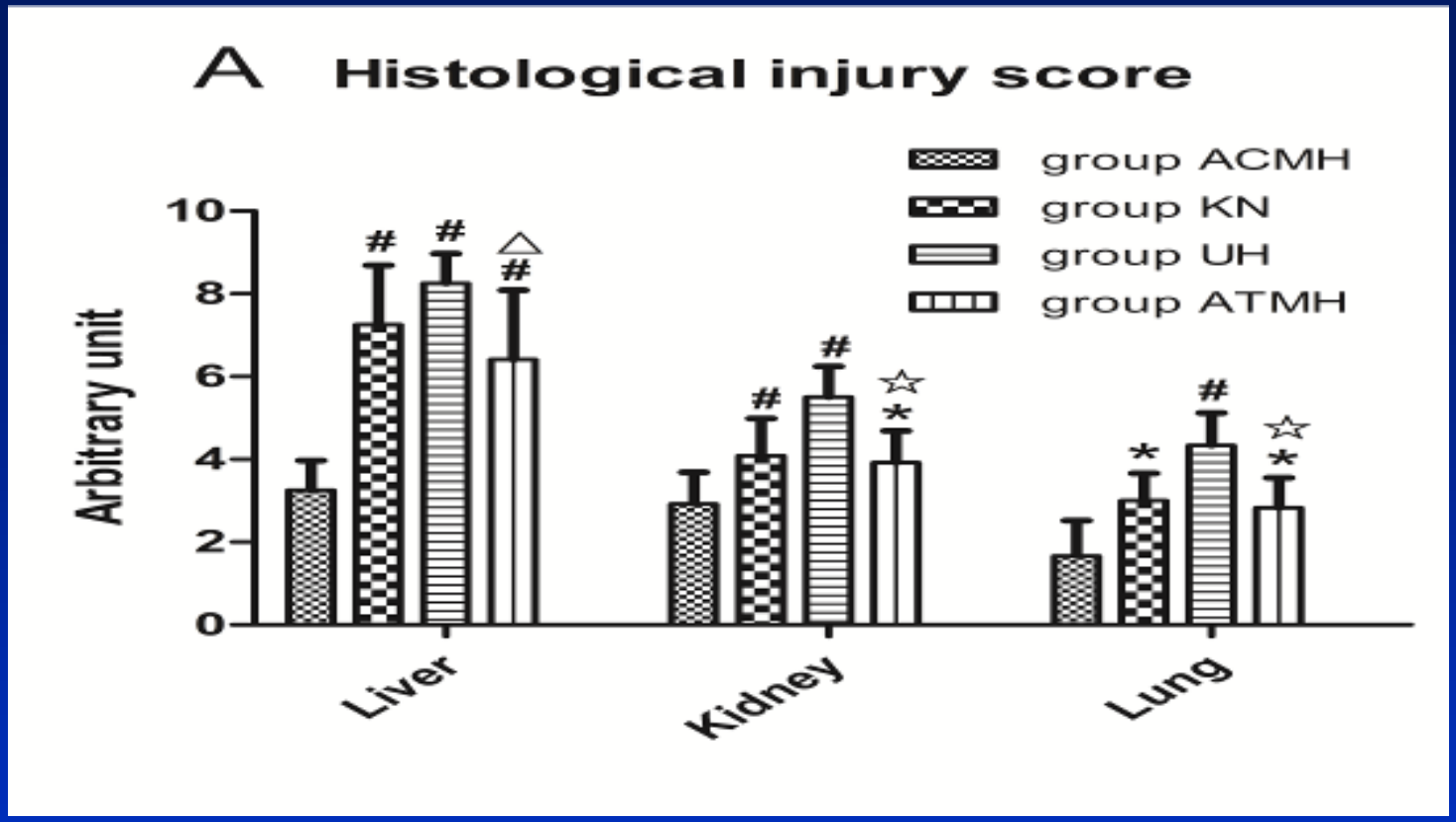


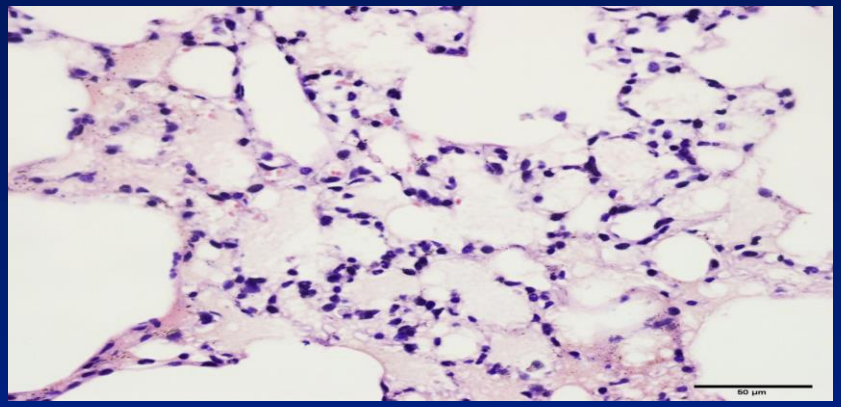
Fig. 3 A, Pathological scores of the lung, liver, and renal damages in the sepsis groups. Significant difference was found between the ACMH group and the other sepsis groups (*$P < .05$, #$P < .01$) as well as between the ATMH group and the UH group ($\triangle P < .05$, $\star P < .01$).

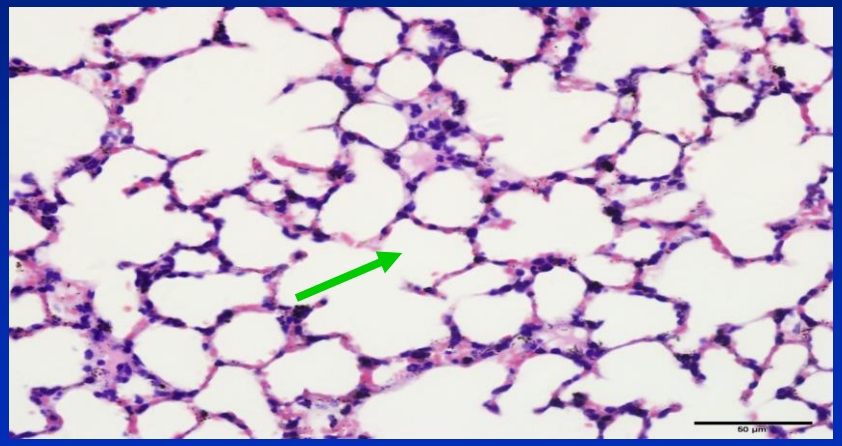
B. Lung

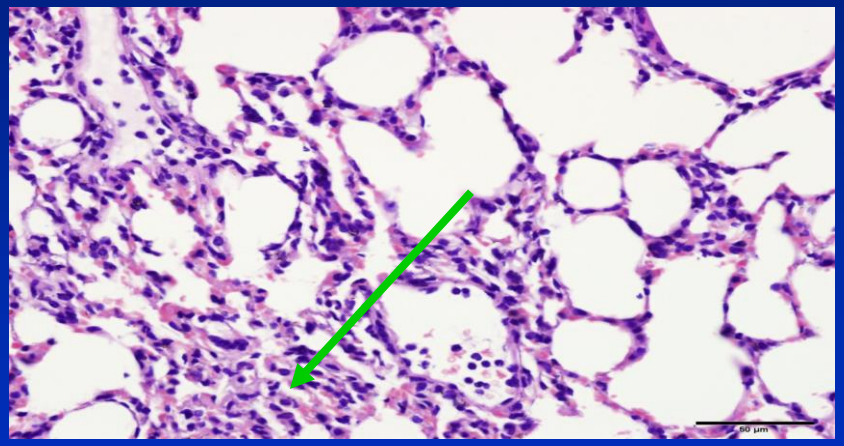
NC

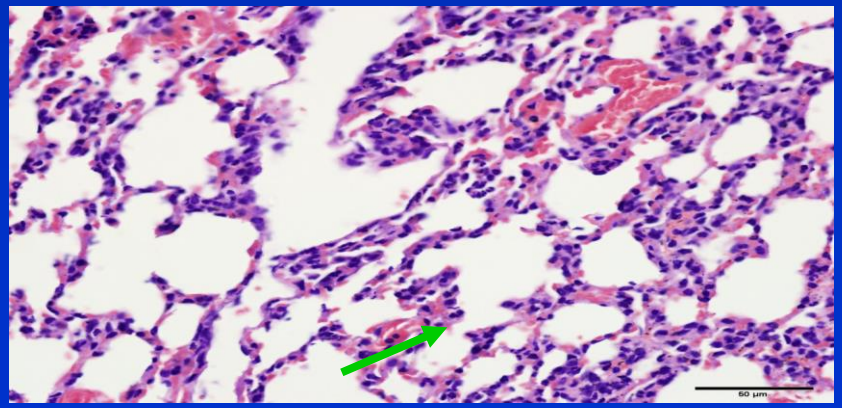
ACMH KN

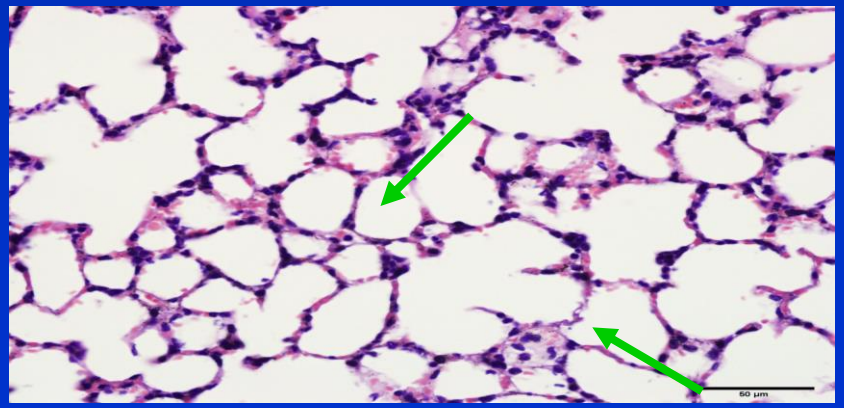
UH ATMH











•ACMH：肺间隔稍增宽，个别炎细胞浸润。

•KN：图片左下角肺泡皱缩，间隔断裂，肺泡内见炎细胞渗出。

•UH:毛细血管充血，肺泡内较多渗出物，间隔较宽，间质细胞增生及炎细胞浸润。

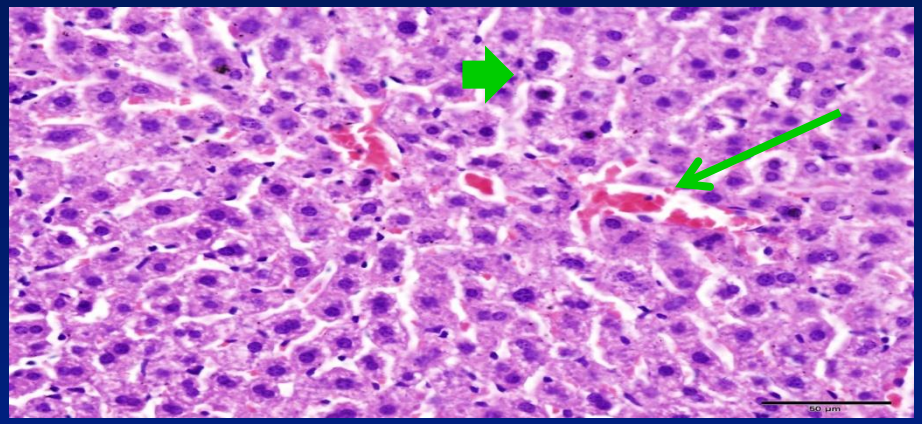
•ATMH：肺间隔稍增宽。

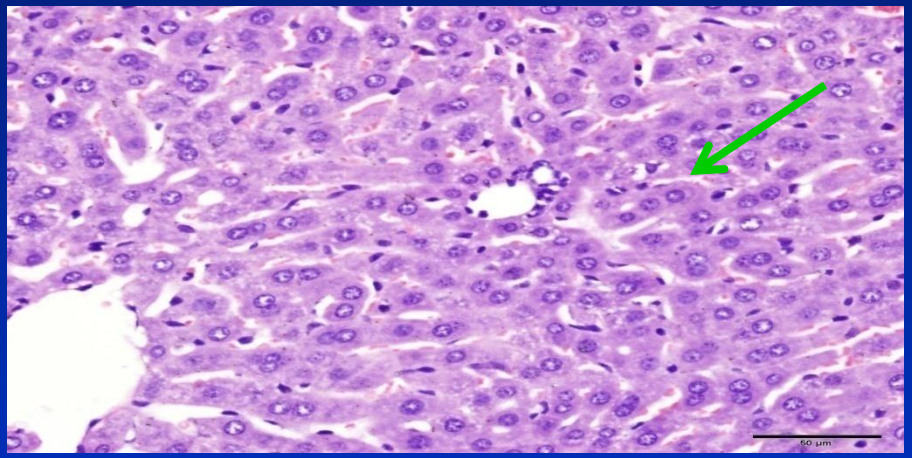
C. Liver

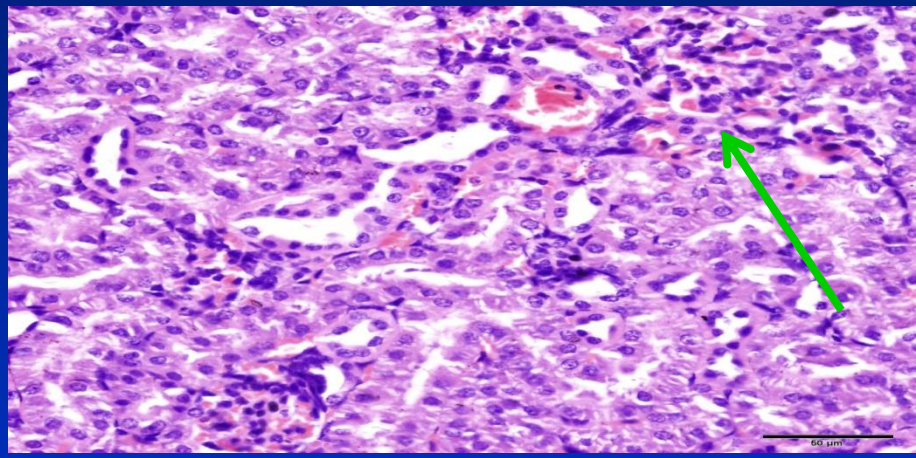
NC

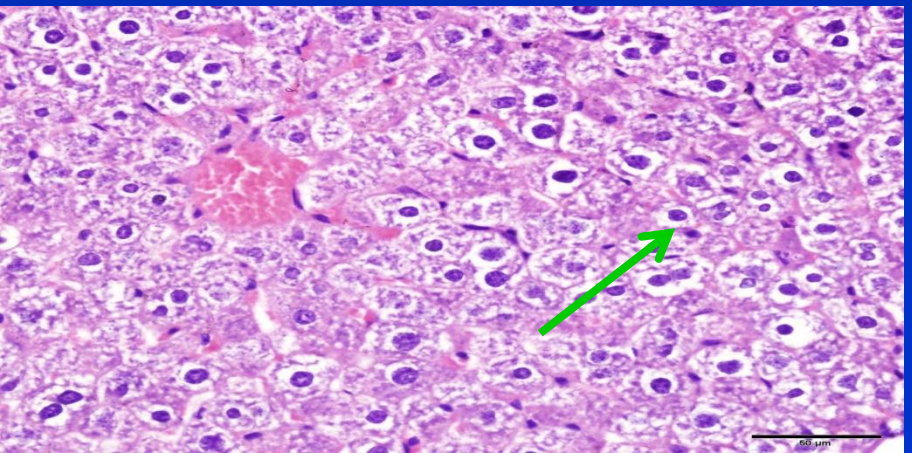
ACMH KN

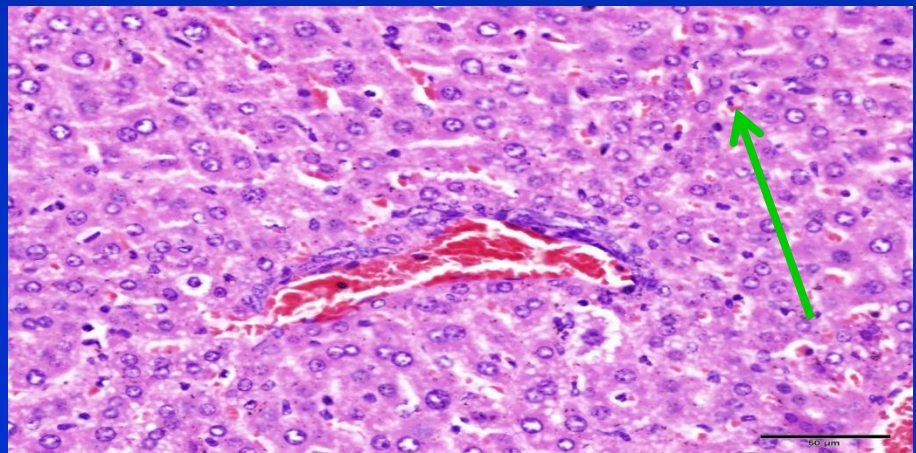
UH ATNH











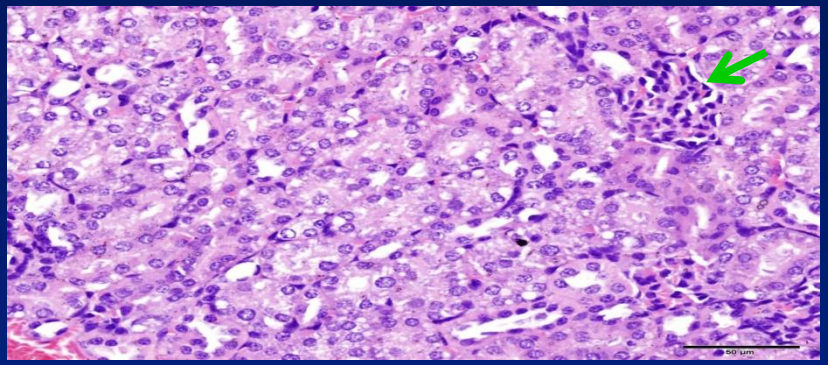
- NC：细箭头-肝中央静脉 ，粗箭头-肝细胞
- ACMH：肝细胞轻度水肿
- KN:肝细胞坏死增生及炎细胞浸润
- UH：肝细胞凋亡坏死增生，核固缩、碎裂。
- ATMH：肝细胞再生，水肿，毛玻璃核。

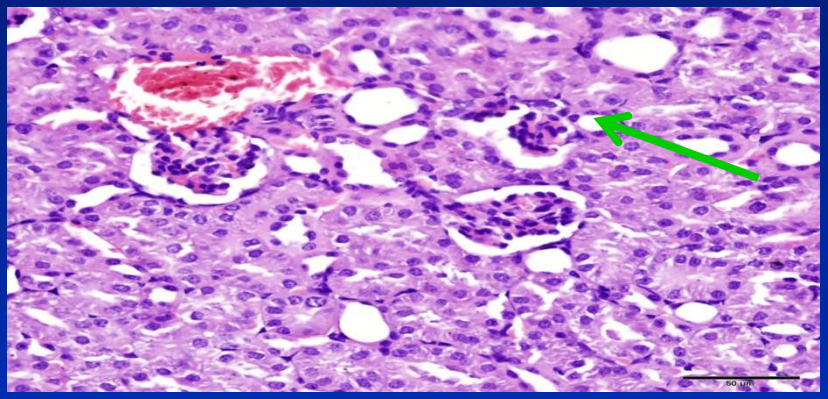
D. Kidney

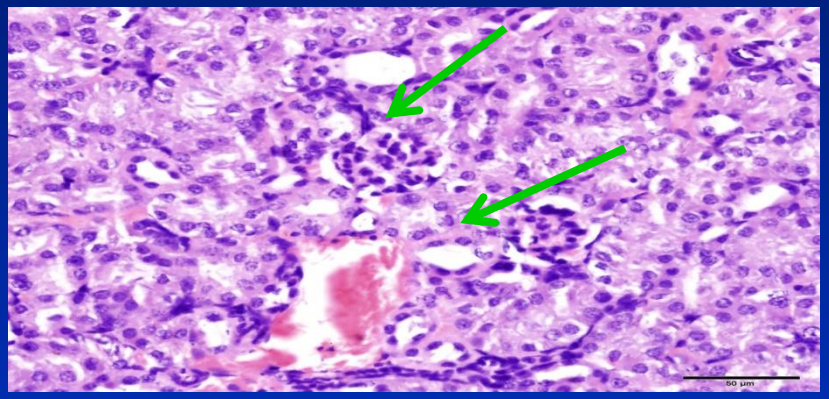
NC

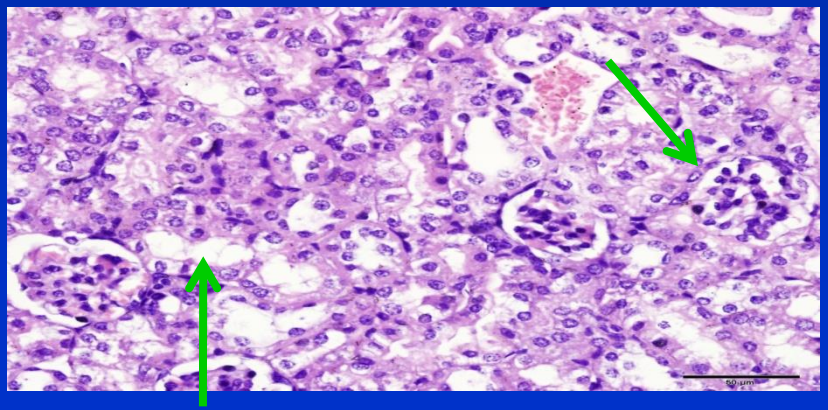
ACMH KN

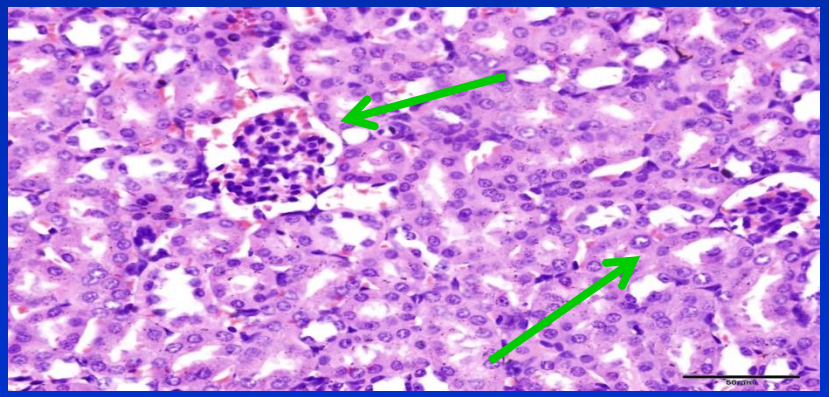
UH ATMH











- NC:肾小球及间质无明显病变
- ACMH:肾小球系膜细胞及基质轻度增生，肾间质水肿
- KN：肾小球细胞数增多，肾小管上皮细胞水肿
- UH：肾小球细胞数明显增多，肾小管扩展，肾小管上皮细胞水肿局灶微绒毛脱落，间质轻度水肿。
- ATMH：肾小球细胞数增多，肾小管轻度扩展，局灶微绒毛脱落，间质轻度水肿。

Discussion

In clinical practice, body temperature variation has been considered as one of the most important diagnostic criteria for several diseases. The temperature increase and decrease are, in certain degree, protective reactions of the body. However, the increase or decrease of the body temperature should be preserved in an appropriate range. Too high or low temperature will result in detrimental effects on the body.

Discussion

Numerous studies have shown that mild hypothermic intervention could significantly reduce the mortality rate of the animals with sepsis. Our study also found that ATMH could reduce the mortality rate of septic mice, but the reduction degree of mortality in septic mice was not as significant as that reduced by ACMH.It is suggesting that the ACMH is beneficial for the prognosis of the septic mice.

Discussion

Several inflammatory factors including TNF-α, IFN-γ and IL-4 could be secreted by multiple immune cells at the stage of sepsis. Our study showed that the serum levels of TNF-α ,IFN-γ and IL-4 were significantly lower in the ACMH group and ATMH group than in the KN group and UH group in some time. The next experiment could be designed to observe more inflammatory markers, to much more fully understand the impacts of ACMH on septic body.

Discussion

Previous studies have shown that about 33% of the patients with sepsis could develop organ failure, among which acute renal failure and renal damages are the most common critical complications for patients with sepsis or septic shock. Several studies have shown that the mild hypothermia therapy could effectively alleviate the acute damages on the heart, liver, and lungs of septic animals.

Discussion

Our results of the present study showed that the ALT, AST, and CREA levels in the ACMH group and the ATMH group were significantly lower than those in the KN group and the UH group; in addition, the levels were lower in the ACMH group than in the ATMH group.

Discussion

Currently, the aim of common treatment for patients with sepsis andACMH is to bring back the body temperature to normal range with the use of heavy blankets or by increasing the environmental temperature via air conditioner. The findings of the present study showed that the state of ACMH is beneficial for the recovery of septic mice.

Discussion

However, only very few studies (especially clinical studies) have investigated the effects of ACMH on patients with sepsis, and a lot of questions including how to maintain the state of ACMH in patients with sepsis, the time of maintaining the state, the possible complications, and how to treat the possible side effects are to be elucidated. The clinical application of ACMH in treating patients with sepsis should be further investigated with multicenter clinical trials with larger sample sizes.

Conclusion

Accompanying mild hypothermia and ATMH could both reduce mortalities in mice with sepsis, and ACMH could reduce mortality even lower, and more alleviate systemic inflammatory responses and the damages in lung, kidney,and other organs were lighter.

In summary

Our experiments suggested that ACMH had significant organ-protective effects. The state of ACMH of the patients with sepsis should be considered, and appropriate management of the temperature should be performed to improve the clinical efficacies in treating patients with sepsis and ACMH.

THANK YOU