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Investigating the potential to assess severe lung inhalation injuries using computed tomography

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ABSTRACT

Purpose: The purpose of this study is to investigate the potential use of computed tomography (CT) in assessing inhalation injuries at various levels by studying the changes in lung imaging of rabbits with severe inhalation injury.
Methods: The sham, serious, critical, and extremely critical lung inhalation injury models were established by the New Zealand white rabbits' inhalation of steam for 0 s, 0.25 s, 0.50 s, and 1.00 s, respectively. Lung CT scans were performed at 1, 4, and 12 h after the administration of steam and a radiologist's scores (RADS) were collected for each CT scan. Lung tissues were later collected to measure the lung wet/dry weight (W/D) ratio and to determine pathological scores. The correlation of the RADS with the lung-tissue pathological scores and W/D changes was investigated.
Results: The RADS and lung-tissue pathological scores are dependent on the time after injury and the level of injury. W/D ratios are dependent on the level of injury. The W/D ratio showed an increasing trend from 1 h to 4 h for the 0.25 s, 0.50 s, and 1 s inhalation injury groups, while the W/D ratio decreased from 4 h to 12 h for the 0.25 s and 0.50 s inhalation injury groups. Further analysis indicates that, at the same time point, the lung RADS positively correlates with both the lung pathological scores and W/D ratios.
Conclusion: A lung CT scan is able to reflect the early-stage lung injuries of rabbits with different levels of severe inhalation injury.

Abbreviations: CT, computed tomography; W/D, wet/dry weight; RADS, radiologist's scores; ARDS, acute respiratory distress syndrome.
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1. Introduction

Among burn patients admitted to the hospital, 20–30% sustain inhalation injuries as well. Inhalation injury alone increases mortality by approximately 20%, with an increase to 60–80% if it is severe [1–3]. Early diagnosis and the grading of inhalation injuries improves therapeutic outcomes for patients [4,5]. There are several modalities for confirming inhalation injury including fiberoptic bronchoscopy, carboxyhemoglobin measurement, radionuclide imaging with 133Xenon, and pulmonary function testing [6–9]. Severe inhalation injuries include damage to the major bronchus and the alveoli, which is primarily determined by a fiber-optic bronchoscope as the main inspection instrument [10]. This does not detect damage in distant airways, respiratory bronchioles, and lung parenchyma. The result provides little predictive value for severe inhalation-injury-induced acute respiratory distress syndrome (ARDS) [11]. A conventional X-ray examination is insensitive to the early stages of an inhalation injury and can only detect severe inhalation injury [12]. ^{133}Xenon scanning is capable of detecting early-stage inhalation injury; however, it cannot determine the severity of the injury [12]. Other examination methods and indicators, such as clinical manifestations, carboxyhemoglobin content, oxygenation index, and extravascular lung fluid content, also cannot provide accurate grading of inhalation injuries [11]. Therefore, further investigation is required into alternative methods for providing early diagnoses of the degree of inhalation injuries.

In the field of lung injury diagnosis, chest computed tomography (CT), in particular, has the advantages that include being intuitive, noninvasive, and repeatable, and is sensitive to identifying the morphological changes associated with lung injuries [13]. A systematic evaluation of thoracic CT scans contributes to diagnosis, prognostic prediction, and therapeutic interventions [14,15]. Despite the studies performed thus far on utilizing CT to diagnose inhalation injuries, it is still unclear whether early-stage changes in lung CT images reflect different levels of inhalation injury. In this study, a rabbit severe steam inhalation injury model has been established and assessed by CT using a radiologist's score (RADS), a lung-tissue wet/dry weight (W/D) ratio, and lung injury histopathology scores. The authors conclude the study by investigating the correlation of early imaging changes with lung injury histopathology and lung W/D changes in order to assess the potential use of Lung CT scan in the diagnosis of different levels of inhalation injury.

2. Materials and methods

2.1. Experimental animals

Sixty-six male New Zealand white rabbits (provided by Guangxi Tiandong Longxiang Rabbit Industry Co., Ltd., license number: SCFK Gui 2014-0003) with ages of six months and weights between 2400 and 2600 g were raised in an environment with a temperature of between 21 and 24°C, a humidity of 50–60%, and a 12-h day-night rhythm, with the freedom to drink and eat ad libitum. All experiments were approved by the Ethics Committee of the No. 181 People's Liberation Army Hospital. All animal experiments complied with the ARRIVE guidelines and was carried out in accordance with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978).

2.2. Experimental classification and model establishment

All rabbits were randomly assigned to a sham injury group (n=18), a serious injury group (n=18), a critical injury group (n=18), and an extremely critical injury group (n=12); according to a previous study, the latter group could not survive up to 12 h, so for this group, no 12-h observation was made [16]. At 1, 4, and 12 h after administering steam, six rabbits were randomly selected from each group, with a lung CT scan, lung W/D measurement, and lung-tissue pathological observation and scoring performed.

The method used to establish the model was consistent with that previously reported [16], whereby, following a 40-mg/kg pentobarbital sodium (Merck, Germany) ear-vein intravenous anesthesia, the rabbit was fixed to the operating table in a supine position. With the right internal jugular vein and right femoral artery dissected and exposed, a 5F double-lumen central-venous catheter and a 3F arterial catheter were inserted, respectively, and were then connected to the monitor through a pressure transducer to monitor the central venous and arterial pressures. The downstream trachea of the cricoid cartilage at the middle of the neck was incised and inserted into a metal tracheal catheter with an internal diameter of 5 mm. An automatic control time and pressure scald instrument (made in our lab, Patent No.: CN200910114104.4) was preheated at the same time of the surgery such that the pressure and temperature inside the autoclave were maintained at 0.02 mPa/cm^2 and 105°C, respectively. All rabbits were then injected with vecuronium (0.04 mg/kg, Chengdu Tiantaishan Pharmaceutical Pty Ltd., China) at the right jugular vein to arrest respiratory for 20 min to protect them from their own respiratory effects. During apnea, an Engströmfob Carestation ventilator (GE, USA) was connected to control the respiration (capacity control mode: tidal volume 10 mL/kg, respiration frequency 50 times/min, inhalation/exhalation ratio 1:1.5, and oxygen concentration 50%). Then continuous infusion of lactated Ringer's solution (Hunan Kelun Pharmaceutical Pty Ltd., China) at 50 ml/h using an infusion pump was used to maintain osmotic balance of the body. Meanwhile, the serious, critical, and extremely critical injury groups each inhaled 0.25 s, 0.50 s, and 1.00 s of steam, respectively, with no inhalation for the sham injury group. A 15-mL/h lactate Ringer's solution (Hunan Kelun Pharmaceutical Pty Ltd.) infusion was continued following the initial 1-h infusion.

2.3. Lhest CT scan and score

A lung CT scan (Discovery CT750 HD, GE, USA) was acquired with the animal fixed in a supine position on a customized wooden stand, followed by the RADS measured on the lung CT images [15]. Briefly, CT scans from each patient were systematically evaluated using 1-cm axial slices from the apex to the level of the diaphragm. The left and right lung fields in each slice were divided into four quadrants, and each quadrant was assigned a score from 0 to 3 corresponding to the severity of the findings. Ten slices were analyzed per animal in each group. The CT scan of a rat was 0.625 mm. Scanning the entire lung produced about 150 CT images. A starting point was selected for each animal's CT image to begin selection of the image. The starting point of different animals should be consistent (based on the part and size of the trachea and bronchus that appears in the CT images). From the starting point image, one picture was selected every four pictures. After selection, pictures showing a fragment of a lung were deleted. Finally, the ten CT pictures were used to calculate a score. The highest, single score within a quadrant was assigned to the final score, and a total score for each slice was calculated. The total scores for ten slices were then summed for the entire CT scan to obtain the overall RADS. To normalize the scores, the average RADS for each CT slide was obtained by dividing the total RADS by the number of CT slices. The CT parameters were: tube voltage of 120 V; tube current of 150 Ma; slice thickness of 0.625 mm; helical pitch of 1.0; lung window and window level of −500 Hu and window width of 2000 Hu.

2.4. Lung W/D

A W/D measurement was taken in accordance with the method provided [17]. Briefly, after the animal was euthanized via an intravenous overdose of pentobarbital sodium (100 mg/kg), its right lung lobe was removed and the surface blood dried with filter paper. The lung lobe was weighed (wet weight), placed in an oven, and weighed daily until the weight was unchanged, indicating the dry weight. The wet/dry weight ratio was then calculated from the wet weight and dry weight values.

2.5. Tissue pathological observation and scoring

Pathological changes in the lung tissues were visualized by hematoxylin and eosin (H&E) staining. The right lung diaphragmatic lobe was extracted. A scalpel then cut straight into the right lung lobe bronchus to divide the temporal lobe into three equal parts of lung tissues. These lung tissues were then immersed in a 4% neutral formaldehyde solution for 48 h before they were embedded in paraffin, cut into 4-μm serial slices with a microtome, and stained with routine hematoxylin-eosin. A BX51 microscope (Olympus, Japan) was used for observation and photographing. For each slice, five random fields were selected for lung-tissue pathological scoring. The scoring method is listed in Table 1 according to a previous study [18].

2.6. Statistical analysis

A statistical analysis of the experimental data was performed using SPSS 19.0 statistical software. The results for the RADS, W/D, and the lung injury histopathology score were expressed as mean ± standard deviation. Meanwhile, the overall comparison used a two-way analysis of the variance, the general group comparison used a one-way analysis of the variance, and the pairwise group comparison used a least significant difference (LSD) test. The correlation between two parameters was analyzed using a Spearman rank correlation analysis. The difference was defined as statistically significant if $p < 0.05$.

3. Results

3.1. Mortality rate

After 6 h, all rabbits in the 1.00 s group died; no rabbits died in the 0.50 s and 0.25 s groups; After 12 h, the rabbit mortality in the 0.50 s group was 25%, and no rabbits died in the 0.25 s group; After 24 h, the rabbit mortality in the 0.50 s and 0.25 s groups were 75% and 25%, respectively.

3.2. Lung CT scan and RADS

Fig. 1A shows the 1-, 4-, and 12-h post-injury CT images for the different rabbit groups. The lungs of the sham injury group were normal at 1 h, 4 h, and 12 h after injury. In the serious, critical, and extremely critical groups, lung interstitial marking and ground-glass opacification were observed at 1 h after injury and increased at 4 h. Additionally, lung interstitial marking and ground-glass opacification had increased in the critical group while had no obvious change in the serious group at 12 h after injury. Lung consolidation was observed at 4 h after injury in the extremely critical group, and at 12 h after injury in the critical group.

The RADS results are shown in Fig. 1B. These results indicate that the RADS significantly increased with time in the serious, critical, and extremely critical groups ($p < 0.05$), except the RADS had no significant change between 1 h and 4 h after injury in the serious group ($p > 0.05$). At the same time point, the RADS significantly increased with an increasing level of

Table 1 – Lung injury pathological scoring standards.

Pathological features	Score 0	Score 1	Score 2	Score 3
Pulmonary interstitial edema	None	Mild, <25% of the observing field	Medium, 25%–50% of the observing field	Severe, >50% of the observing field
Alveolar edema	None	Mild, <25% of the observing field	Medium, 25%–50% of the observing field	Severe, >50% of the observing field
Inflammatory cell infiltration	None	Mild	Medium	Severe
Alveolar hemorrhage	None	Mild, <25% of the observing field	Medium, 25%–50% of the observing field	Severe, >50% of the observing field
Transparent membrane formation	None	Mild, <5% of the observing field	Medium, 5%–25% of the observing field	Severe, >25% of the observing field

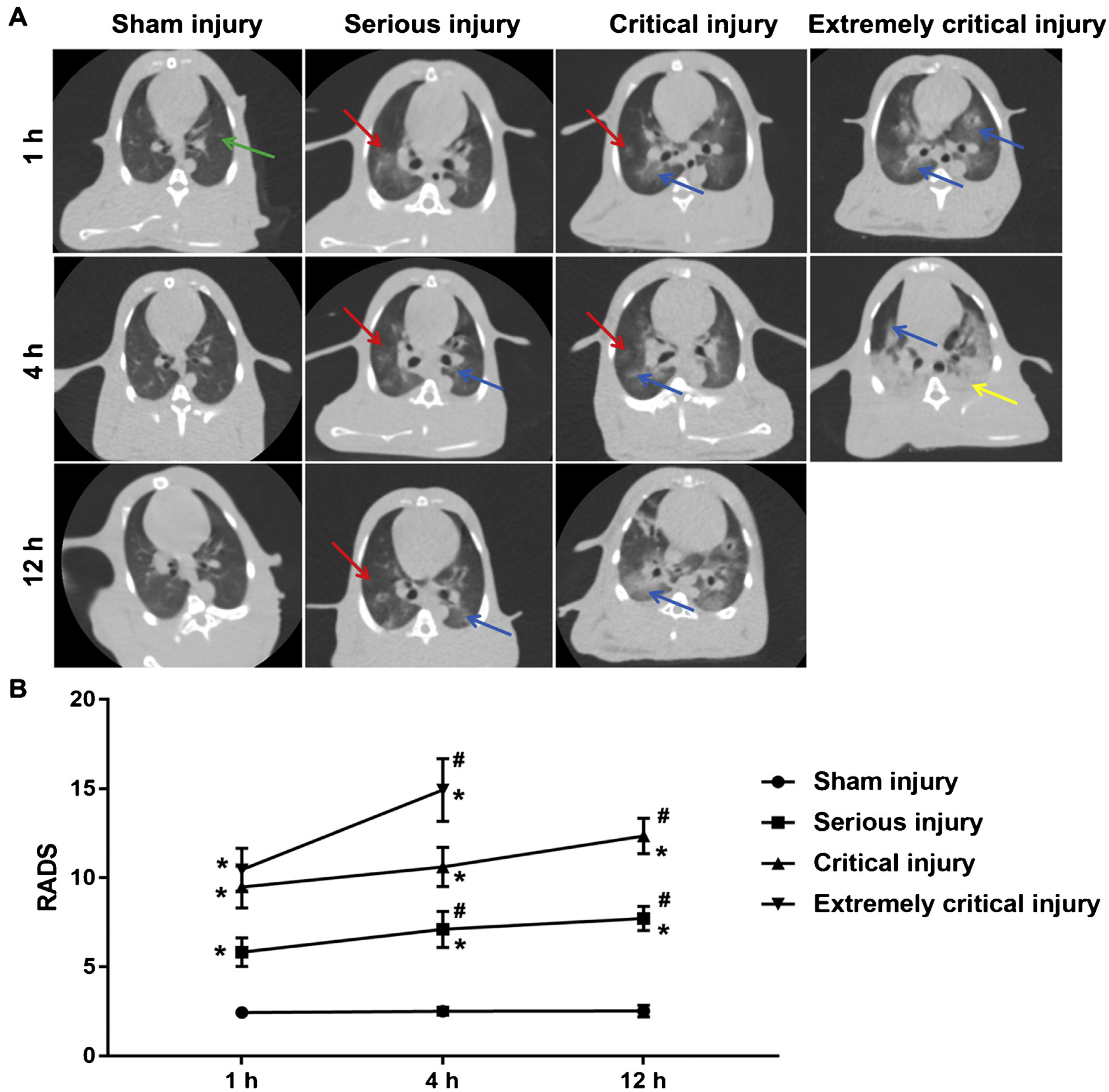

Fig. 1 – CT scans and RADS results at 1, 4, and 12 h post injury for different groups of rabbits. (A) The 1-, 4-, and 12-h post-injury CT images for different rabbit groups. (B) The RADS results for different rabbit groups. *p < 0.05 vs sham group at the same time point. #p < 0.05 vs 1 h at the same group. The red arrow indicates lung interstitial marking, the blue arrow indicates ground-glass opacification, the yellow arrow indicates lung consolidation, and the green arrow indicates normal tissues. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

injury ($p < 0.05$). The RADS displayed a correlation with both the time and level of injury.

3.3. *Lung W/D*

Fig. 2shows the W/D at 1, 4, and 12 h post injury for the different rabbit groups. The W/D remains consistent at 1, 4, and 12 h post injury within the sham injury group. At the same time point, the W/D tends to significantly increase with an increasing level of injury ($p < 0.05$), except the W/D had no significant change between the sham and serious groups at 1 h after injury ($p > 0.05$). Within the same group, the RADS significantly increased with time in the serious, critical, and extremely critical groups ($p < 0.05$), except the RADS had no significant change between 1h and 12h after injury in the serious group ($p > 0.05$). Additionally, the 4-12-h W/D ratio shows a slightly decreasing trend, however, the difference is not significant ($p > 0.05$).

3.4. *Lung-tissue pathological observation and scoring*

Fig. 3A shows the H&E images at 1, 4, and 12 h after injury for the different rabbit groups. The lungs of the sham injury group

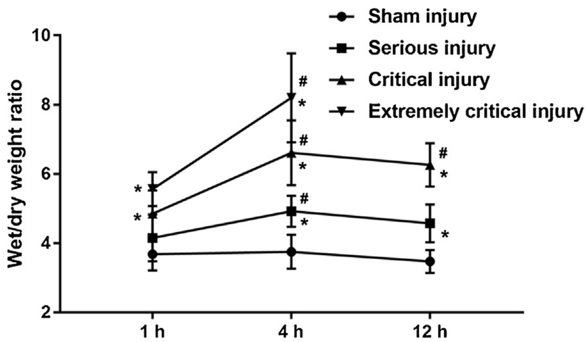

Fig. 2 – W/D at 1, 4, and 12h post injury for different rabbit groups. *p<0.05 vs sham group at the same time point. #p<0.05 vs 1h at the same group.

were normal at 1h, 4h, and 12h after injury. In the serious group, slight alveolar hemorrhage, inflammatory cell infiltration, AND pulmonary interstitial edema were observed at 1h after injury. This increased at 4h after injury while there was no change at 12h after injury. Additionally, slight alveolar septum thickening was observed at 4h after injury and increased at 12h after injury. Obvious alveolar hemorrhage, inflammatory cell infiltration, pulmonary interstitial edema, and slight alveolar septum thickening were observed at 1h after injury and gradually increased at 4h and 12h after injury in the critical group. Obvious alveolar hemorrhage, inflammatory cell infiltration, pulmonary interstitial edema, and alveolar septum thickening were observed at 1h after injury and increased at 4h after injury in the extremely critical group.

Fig. 3B shows a lung-tissue pathological score comparison at 1, 4, and 12h post injury for the different rabbit groups. At the same time point, the lung-tissue pathological scores of the different groups all tended to increase with an increasing level of injury ($p<0.05$). Within the same group, the lung-tissue pathological scores significantly increased with time in the serious, critical, and extremely critical groups ($p<0.05$) except the lung-tissue pathological scores had no significant change between 1h and 4h after injury in the critical group ($p>0.05$). The lung-tissue pathological score is dependent on the time and level of injury.

3.5. *Correlation of lung RADS with lung pathological score and W/D changes for different levels of injury*

Table 2 lists the correlation of the lung RADS with pathological scores and W/D changes for different levels of injury. From the table, it can be seen that for different injury levels, at the same time point, the lung RADS is positively correlated with the lung pathological score and W/D. Additionally, the 1h RADS is positively correlated with the ultimate W:D and lung pathological score at 12h.

4. Discussion

Compared with traditional X-ray films, the lung CT had a higher density resolution and powerful image post-processing functions. It used the best brightness and contrast to more accurately reflect the presence of lesions, which is helpful for accurately judging the degree and extent of lung damage, and the dynamic changes and distribution of small lesions. A number of studies have been performed using lung CT to diagnose inhalation injuries. Reske et al. used CT to examine a patient with burns and severe inhalation injuries, and found pulmonary ground-glass opacification and consolidation 12h after injury [19]. Oh et al. analyzed the RADS scores of CT scans of patients with various inhalation injuries, and, in conjunction with bronchoscopy, they were able to increase the inhalation injury diagnosis by 12.7 times [15]. Typical lung CT images of ARDS patients demonstrated not only ground-glass opacification, but also lung consolidation, which was more obvious in the lower lobe of the lung. Their distributions depended on the severity of the ARDS, where the area of lung consolidation and the extent of ground-glass opacification both increased with severity [20,21]. All of the above studies evaluated the potential use of CT in assessing the degree of inhalation injury.

However, previous studies have included inhalation injury as a whole without grading the extent of lung injury. Therefore, the role of CT in evaluating the different levels of severe inhalation injury was not studied. In this study, we established the models including serious, critical, and extremely critical lung injury to investigate the effect of CT on evaluating the degree of inhalation injury. We found that an increasing level of injury and an extended time after injury resulted in an increase of lung marking and ground-glass opacification, with some lung consolidation observed in the extremely critical injury group. Within the same group, the RADS increased with increasing time after injury as well as with increasing level of injury, suggesting that the RADSs were closely correlated to the level of injury and the injury time. Similar results were achieved; lung CT images could accurately reflect the presence of lesions. Additionally, this study found that lung CT images could reflect the severity degree of inhalation injury.

The lung pathological examination and W/D are direct measures of the level of lung injury, as they can accurately assess the degree of lung tissue damage [22,23]. This study found that, at the same time point, W/D tended to increase with an increasing level of injury. Among the three injury groups, W/D increased from 1h to 4h after injury, but then decreased slightly at 12h, although the difference between 4h and 12h was not significant. However, it is unclear why this phenomenon occurs, it may be related to the absorption of excessive lung fluid by the lung itself. This study also found that with increasing time and level of injury, the lung-tissue pathological score increased significantly, demonstrating an obvious dependence. The above results confirmed that the lung-injury stratified animal model was successfully replicated. Further analysis of the correlation of the RADS with the lung-tissue pathological score and lung W/D for different levels of inhalation injury indicated that at 1, 4, and 12h after injury, the RADS demonstrated a significant positive correlation with the lung-tissue pathological score and lung wet/dry changes. This result indicates that the trend of the RADS was consistent with that of the lung pathological scores and the lung W/D ratios. As a result, a CT scan is able to reflect the early-stage lung injuries of patients with different levels of severe inhalation injury, and has the potential to provide a quantitative assessment for these patients.

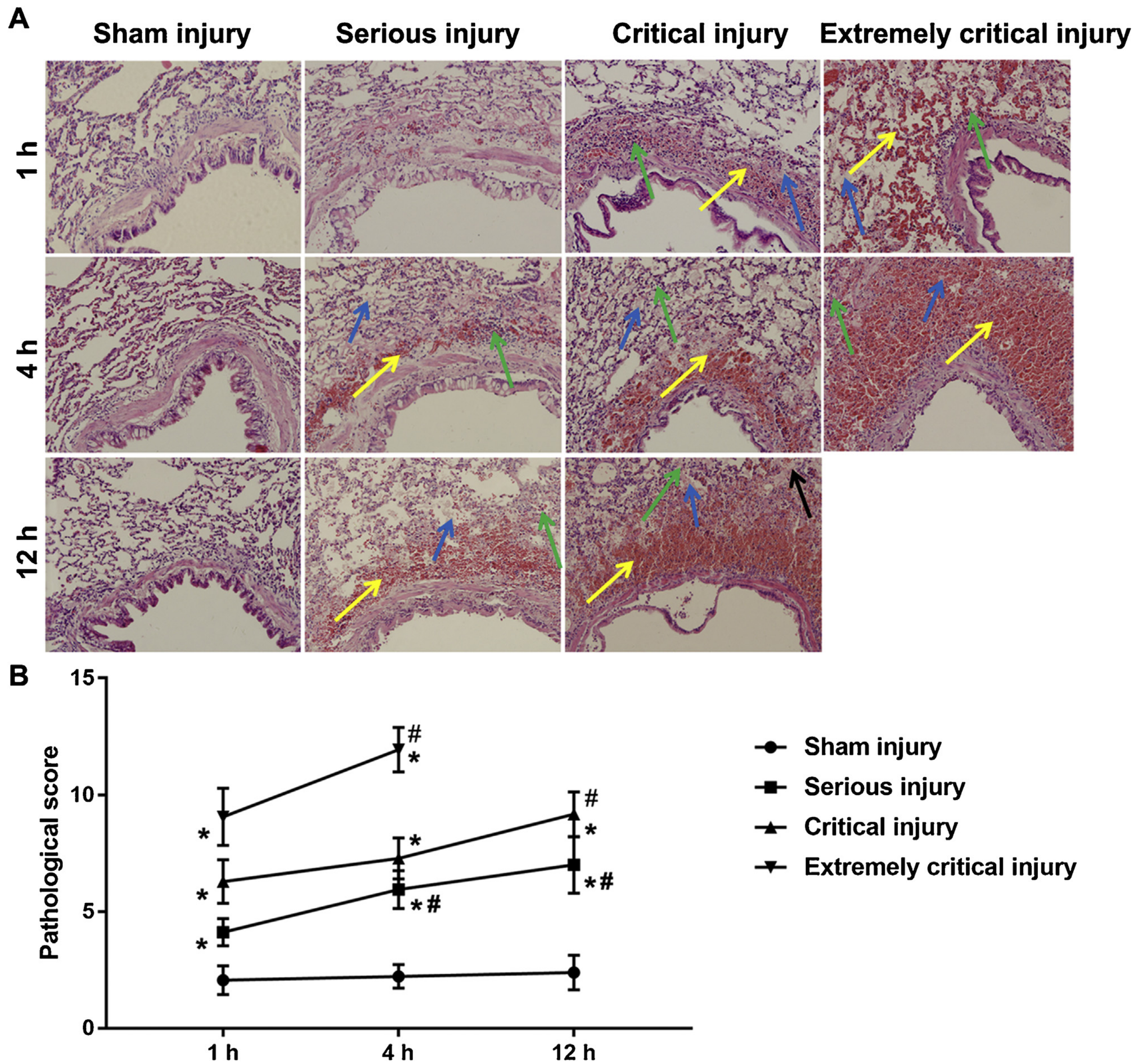

Fig. 3 – Lung tissue pathological observation and score at 1, 4, and 12 h post injury for different rabbit groups. (A) The H&E images at 1, 4, and 12 h after injury for the different groups (H&E × 200). (B) Lung-tissue pathological score at 1, 4, and 12 h after injury for the different groups. *p < 0.05 vs sham group at the same time point. #p < 0.05 vs 1 h at the same group. The blue arrow indicates alveolar edema, the green arrow indicates inflammatory cell infiltration, the yellow arrow indicates alveolar hemorrhage, and the black arrow indicates transparent membrane formation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2 – Correlation of lung RADS with pathological scores and W/D changes.

Groups		RADS		
		1h	4h	12h
Pathological scores	1h	0.885	–	–
	4h	–	0.920	–
	12h	0.872	–	0.868
W/D	1h	0.718	–	–
	4h	–	0.914	–
	12h	0.870	–	0.911

This study has several limitations. Firstly, in the absence of P/F ratios, the presence of ARDS cannot be accurate inferred. But in the previous research we found that the F/P ratio is less than 300mmhg at 4h in the serious critical group and at 1h in critical and extremely groups [16]. Furthermore, small lesions with little or no density change or early lesions only occurring at the cellular level are difficult to detect by CT scan. Therefore, a CT scan may have errors in the diagnosis of early lung injury. Secondly, because of the rapid development of severe lung injury, the relationship between the CT and lung injury progression remains to be studied further. Moreover, steam and smoke are two common pathogenic factors in establishing models of inhaled lung injury. Smoke inhalation damage and vapor inhalation damage are very different; smoke inhalation damage is mainly chemical damage, and vapor inhalation damage is physical damage. It can only be considered that both can cause similar pathological changes of ARDS according to histopathological findings of lung tissue [9,24]. We used steam as a causative factor in the design of the experiment because the induction factor was single and the experiment was highly reproducible. In future, burn- and smoke-induced (carbon monoxide/cyanide inhalation) lung injury may be used to study the effect of CT on evaluating the degree of inhalation injury.

In summary, this study shows that CT can be used to assess different levels of inhalation injury in rabbits. In future, larger multicenter prospective studies are required to validate CT criteria for the grading of severe inhalation injury in order to provide important evidence for the early-stage diagnosis and grading of severe inhalation injuries.

4.1. *Declarations of interest*

None.

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