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# Clinical outcomes of pleural drainage on pneumothorax and hydrothorax in critically ill patients with COVID-19: A case series with literature review



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## ABSTRACT

**Background:** For patients with COVID-19, pneumothorax and hydrothorax are suggested to be negative prognostic indicators. However, the management of these two conditions has rarely been discussed. We aimed to describe the clinical outcomes of pleural drainage in critically ill patients with COVID-19.

**Methods:** A total of 17 pleural drainages were performed in 11 critically ill patients with pneumothorax or hydrothorax. Either chest tubes or central venous catheters (CVCs) were used. The clinical outcomes, including respiratory and circulation indicators at 24 h and 1 h before the procedure and 24 h and 48 h after the procedure, were retrospectively recorded.

**Results:** (1) Following pleural drainage, there was a 19.1% improvement in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio from 147.4 mmHg (-1 h) to 175.5 mmHg (24 h), while the mean positive end expiratory pressure (PEEP) decreased from 10.7 cmH<sub>2</sub>O (-1 h) to 8.9 cmH<sub>2</sub>O (24 h) and 8.1 cmH<sub>2</sub>O (48 h). The A-a gradients decreased from 313.3 mmHg (-1 h) to 261.3 mmHg (24 h). (2) The dosage of norepinephrine increased from 0.15 μg/kg/min (-1 h) to 0.40 μg/kg/min (24 h). (3) No haemorrhagic or infectious complications were observed. (4) A total of 41.6% of CVCs were partially or fully obstructed, while no chest tubes were obstructed.

**Conclusion:** For critically ill patients with COVID-19, pleural drainage leads to a significant improvement in oxygenation and gas exchange, but the deterioration of circulation is not reversed. It is safe to perform pleural drainage even though anticoagulation therapy and glucocorticoids are widely used. Chest tubes rather than CVCs are recommended.

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## Background

On March 19, 2020, the WHO characterized coronavirus disease 2019 (COVID-19) as a global pandemic. As of Oct 25, 2020, the widespread human-to-human transmission of SARS-CoV-2 has resulted in > 4,283,000 cases, with > 1,150,000 deaths. The clinical severity of COVID-19 varies greatly, from asymptomatic to death. Pneumothorax and hydrothorax have been reported in patients with COVID-19, especially in critically ill patients. Although it has been suggested that pneumothorax can cause death<sup>1</sup> and hydrothorax is a negative prognostic indicator,<sup>2</sup> the

management of these two conditions is rarely discussed. Though pleural drainage has been widely used for many patients without COVID-19, concerns about the safety and efficacy of this procedure may arise regarding patients with COVID-19, especially when the patient's general condition is complicated. It remains unclear whether pleural drainage is safe, when to offer the procedure, and whether patients would benefit from it.

During the outbreak of COVID-19, the number of critically ill patients exceeded the capacity of local hospitals in Wuhan, China. Several provisional intensive care units (ICUs) designated for critically ill patients with COVID-19 were thus established. When patients in general wards had respiratory distress and/or hypoxemia even after receiving standard oxygen therapy or non-invasive mechanical ventilation, they would be transferred to the ICU ward and receive tracheal intubation. Our medical team, which came from our hospital, provided comprehensive medical support in one of the provisional ICUs. In this study, we aimed to clarify the characteristics of patients with pneumothorax and hydrothorax and evaluate the safety and efficacy of pleural drainage.

**Abbreviations:** COVID-19, coronavirus disease 2019; ICU, intensive care unit; FiO<sub>2</sub>, fraction of inspired oxygen; CXR, chest X ray; CVC, central venous catheter; cTNI, cardiac troponin I; CKMB, creatine phosphokinase-Mb; NT-proBNP, N terminal pro B type natriuretic peptide; P[A-a]O<sub>2</sub>, alveolar-arterial oxygen pressure difference; MAP, mean arterial pressure; IQR, interquartile range; SD, standard deviation; APTT, activated partial thromboplastin time; Alb, albumin; P/F, PaO<sub>2</sub>/FiO<sub>2</sub>; PEEP, positive end expiratory pressure

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## Methods

### Patients

This single-centre, retrospective, observational study was conducted in the provisional ICU of Tongji Hospital (Wuhan, China). A total of 109 critically ill patients with COVID-19 were admitted to the ICU from February 4, 2020 to April 14, 2020. Laboratory confirmation of a SARS-CoV-2 infection was performed by the local health authority using RT-PCR of nasopharynx swab samples. Critically ill patients were defined as those who required mechanical ventilation or had a fraction of inspired oxygen (FiO<sub>2</sub>) of at least 60%. The patients would be intubated based on Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (5<sup>th</sup> to 7<sup>th</sup> edition). All patients with pleural drainage were retrospectively reviewed and analysed. The study was approved by the Institutional Ethics Committee of our hospital. The requirement for written informed consent was waived, as this was a retrospective observational study.

### Procedures

Bedside chest X ray (CXR), bedside lung ultrasound or chest CT were performed to evaluate the chest conditions of all critically ill patients. The decision to perform drainage was made by the clinical team in charge of the patient. Generally, the indications for pleural drainage included the following: (1) any pneumothorax (with mechanical ventilation) confirmed by CXR or CT; (2) large pleural effusion (> 800 mL) estimated by CXR, CT or ultrasound, despite aggressive treatment of the underlying diseases (e.g.,

congestive heart failure, hypoproteinaemia); or (3) moderate pleural effusion (500–800 mL) with significant symptoms caused by the effusions (e.g., exacerbation of respiratory distress or circulation). The application of anticoagulation and glucocorticoids was not considered a contraindication. Patients with occult pneumothorax (defined as pneumothorax shown only on CT and not suspected on CXR) or small pleural effusion (< 500 mL) did not undergo pleural drainage.

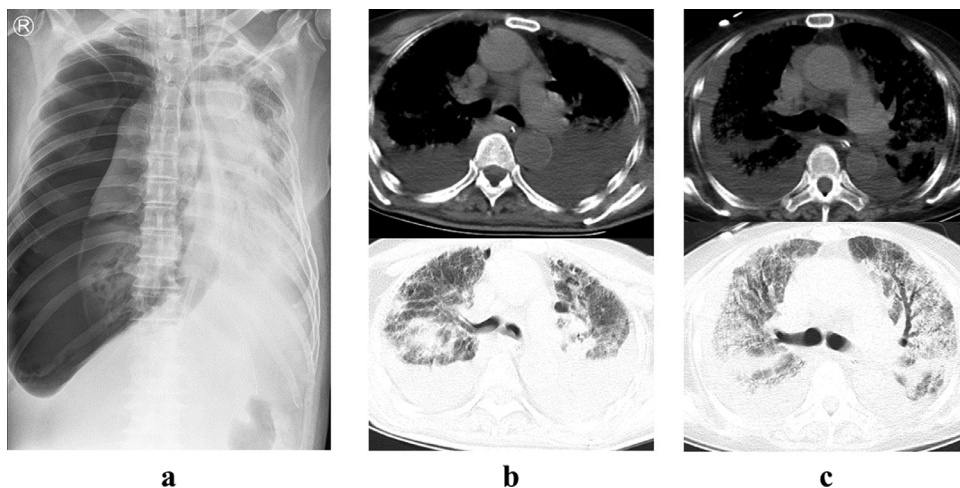
For patients with pneumothorax, large-bore chest tubes were inserted. For patients with hydrothorax, either ultrasound-guided central venous catheters (CVCs) or chest tubes were inserted, depending on the operators' preferences (If a thoracic surgeon was present, the chest tube would be selected. If not, an ICU physician would insert a CVC rather than waiting for the surgeon). The size of the chest tube depended on the supply, as we sometimes faced material shortages. Chest tubes were connected to water seal chest drainage systems, and CVCs were connected to drainage bags. The drainage tubes were left to drain freely, and the volume of drainage was recorded daily. All procedures were performed by experienced thoracic surgeons or ICU physicians at the bedside.

### Data collection

Epidemiological, clinical, laboratory, treatment, and outcome data were obtained from medical records, nursing records, laboratory findings, and radiological examinations. Clinical outcomes were followed up to April 13, 2020. Notably, respiratory indicators (e.g., ventilator settings, PaO<sub>2</sub>, FiO<sub>2</sub>, PaCO<sub>2</sub>) and circulation indicators (e.g., blood pressure, amount of norepinephrine, lactate, cardiac troponin I

**Table 1**  
Baseline characteristics of the patients.

Subject	Gender	Age	Smoking Index	lung surgery history	Indication	Clinical endpoint	Duration from onset to endpoint	Imaging	CT score
1	M	65	150	no	pneumothorax	Death	40	CXR+CT	12
2	M	69	0	no	hydrothorax	Transferred out	79	CT	17.5
3	M	51	0	no	pneumothorax	Death	30	CXR	/
4	M	70	0	no	hydrothorax	Transferred out	75	CXR+CT	22.5
5	F	56	0	yes	both	Death	25	CXR+CT	12
6	F	71	0	no	hydrothorax	Death	31	CXR	/
7	M	67	0	no	both	Death	28	CXR	/
8	F	80	0	no	hydrothorax	Death	62	CXR+CT	24.5
9	M	66	800	no	hydrothorax	Transferred out	78	CXR+CT	10
10	F	67	0	no	both	Death	79	CXR+CT	18
11	M	77	0	no	hydrothorax	Death	96	CT	13.5



**Fig. 1.** Typical images of pneumothorax (a) and hydrothorax (b and c) in patients with COVID-19. (a), CXR of subject 1. (b) and (c), Axial chest CT of subjects 4 and 8, respectively. Consolidation and air bronchogram were diffusely involved in the bilateral lungs.

(cTnl), creatine phosphokinase-Mb (CK-MB), N terminal pro B type natriuretic peptide (NT-proBNP)) were recorded 24 h before the procedure (-24 h), 1 h before the procedure (-1 h), 24 h after the procedure (24 h) and 48 h after the procedure (48 h). The alveolar-arterial oxygen pressure difference (P[A-a]O<sub>2</sub>) was calculated using the assumption of a respiratory quotient of 0.8. Mean arterial pressure (MAP) was calculated as 1/3 the systolic blood pressure plus 2/3 the diastolic blood pressure. Chest CT were evaluated with CT scores described in Pan et al.'s article.<sup>3</sup> Light's criteria were used to determine if the pleural effusion was transudative or exudative. A drainage tube that drained no gas or effusion fluid was considered fully obstructed. A drainage tube that only partially drained gas or effusion fluid was considered partially obstructed.

**Statistical analysis**

Data were summarized as counts, proportions, and percentages; means with standard deviations (SDs); and medians with interquartile ranges (IQRs), as appropriate. Wilcoxon matched-pairs signed-ranks tests were used to compare respiratory and circulatory indicators, as most of these variables were nonparametric data. The tests were two-sided with significance set at a *p* value less than 0.05.

**Results**

**Baseline data**

Eleven patients (7 males and 4 females) who underwent 17 pleural drainages were enrolled in the study. The baseline characteristics are listed in Table 1. The mean age was 67.2±7.9 years. Two males were smokers. All the patients were receiving mechanical ventilation when pleural drainages were performed. Two patients (18.2%) were identified with pneumothorax only, 6 (54.5%) with hydrothorax only, and 3 (27.3%) with both. The mortalities of these patients were 100%, 50% and 100%, respectively. Eight patients (72.7%) died, with a median course of 35.5<sup>16</sup> days. Three patients (27.3%) were transferred out of the ICU, with a median course of 78<sup>2</sup> days.

For imaging examination, 3 patients had only CXR, 2 patients had only CT, and the rest 6 patients had both CXR and CT. Ground glass opacities (GGO), crazy-paving pattern (GGO with superimposed inter- and intralobular septal thickening), linear opacities and consolidation were frequently observed (Fig. 1). The CT scores were from 10 to 24.5 points, with a median of 15.5 points. CXR showed multiple GGOs and infiltration in both lungs.

The clinical features and indications for pleural drainage are shown in Table 2. Four (44.4%) drainages were on the right, 3 (33.3%) were on the left, and 4 (44.4%) were bilateral. Regarding the indications for the 17 pleural drainages, 3 (17.6%) were pneumothorax, 11 (64.7%) were hydrothorax, and 3 (17.6%) were both. Eight patients had CT scans, and all of them had lung parenchymal alterations with different severity. No bulla emphysema or pneumomediastinum was identified. None of the pneumothorax occurred after pleural drainage. Chest tubes sized 14Fr to 30Fr were used in 5 (28.4%) drainages, and none of them were obstructed. CVCs were used in 12 (70.6%) drainages; 3 (25.0%) were partially obstructed, and 2 (16.7%) were fully obstructed. For subject 8, a second pleural drainage was performed due to obstruction of the first CVC. The median total volume of drainage in 48 h for hydrothorax was 1215 (935) ml. Pleural effusions were collected and tested in 7 drainages. All the effusions were exudate using the Light criteria and were negative in the bacterial culture. Glucocorticoids and therapeutic antibiotics were used in 9 (52.9%) and 13 (76.5%) drainages, respectively. Anticoagulation therapy was used for 12 (70.6%) drainages, with an activated partial thromboplastin time (APTT) ranging from 45 to 70 s. For patients without anticoagulation therapy, the APTT ranged from 42 to 53 s.

**Table 2**  
Clinical characteristics and indications of pleural drainage.

Subject No	Study Side	Indication	Duration from onset to intubation	Duration from intubation to drainage	Size	Patency degree	Light criteria	Volume of drainage in 48h (mL)	Bacterial culture	Glucocorticoid	Therapeutic antibiotic	Anti-coagulation	Lung parenchymal alterations on CT	APTT (s)	Alb (g/L)
1	right	pneumothorax	21	11	18Fr	unobstructed	/	345	/	yes	yes	yes	NP	50	31.8
2	left	hydrothorax	24	32	CVCs	unobstructed	exudate	2450	-	yes	yes	yes	yes	60	30.8
3	right	hydrothorax	26	32	CVCs	unobstructed	exudate	0	-	yes	yes	yes	yes	60	30.8
4	right	pneumothorax	10	0	30Fr	unobstructed	/	1120	/	no	yes	no	yes	45	28.5
5	right	hydrothorax	10	37	CVCs	unobstructed	exudate	1800	-	no	yes	yes	NP	45	37.9
6	left	hydrothorax	14	45	CVCs	unobstructed	/	2100	/	no	yes	yes	yes	45	37.9
7	right	hydrothorax	14	2	CVCs	moderate	exudate	400	-	yes	yes	yes	yes	50	23.0
8	right	both	11	9	24Fr	unobstructed	/	30	/	yes	yes	yes	yes	55	29.4
9	right	hydrothorax	11	12	CVCs	moderate	/	1300	/	no	no	no	NP	42	36.2
10	left	hydrothorax	19	12	CVCs	obstructed	/	400	/	no	no	no	yes	42	36.2
11	left	both	19	4	CVCs	moderate	/	1130	/	no	no	no	yes	53	25.1
12	right	pneumothorax	41	7	14Fr	unobstructed	/	345	/	no	no	yes	yes	70	26.4
13	right	hydrothorax	41	16	CVCs	obstructed	exudate	2450	-	yes	yes	yes	yes	60	35.2
14	right	hydrothorax	27	18	CVCs	unobstructed	/	0	/	yes	yes	yes	yes	60	37.4
15	left	hydrothorax	27	10	CVCs	moderate	/	1120	/	no	yes	yes	yes	41	37.2
16	left	both	24	44	24Fr	unobstructed	exudate	1800	-	yes	yes	no	yes	45	29.2
17	left	hydrothorax	65	19	CVCs	unobstructed	exudate	2100	-	No	Yes	Yes	yes	50	30.0

CVCs, central venous catheters; NP, not performed.

Hypoproteinaemia (defined as serum albumin (Alb) less than 35 g/L) existed in 7 (77.8%) patients. Typical images are shown in Fig. 1.

### Efficacy

The respiratory data are shown in Fig. 2. Oxygenation significantly improved, as the PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio increased from 147.4 mmHg (-1 h) to 175.5 mmHg (24 h,  $P = 0.013$ ), while the mean positive end expiratory pressure (PEEP) decreased from 10.7 cmH<sub>2</sub>O (-1 h) to 8.9 cmH<sub>2</sub>O (24 h,  $P = 0.024$ ) and 8.1 cmH<sub>2</sub>O (48 h,  $P = 0.042$ ). The effects on the PEEP were sustained for the full 48 h after the procedure. Similarly, P[A-a]O<sub>2</sub> decreased from 313.3 mmHg (-1 h) to 261.3 mmHg (24 h,  $P = 0.013$ ), suggesting an improvement in gas exchange. PCO<sub>2</sub> increased from 52.5 mmHg (-24 h) to 57.5 mmHg (-1 h,  $P = 0.049$ ) and did not significantly fall after the procedure (Fig. 2).

The analysis showed that pleural drainage was unable to reverse circulatory deterioration (Fig. 3). The dosage of norepinephrine increased from 0.15  $\mu\text{g}/\text{kg}/\text{min}$  (-1 h) to 0.40  $\mu\text{g}/\text{kg}/\text{min}$  (24 h,  $P = 0.027$ ), while the MAP remained unchanged. Lactate also increased from 1.23 mmol/L (-24 h) to 1.77 mmol/L (48 h,  $P = 0.021$ ). NT-proBNP increased from 2549 ng/ml (-1 h) to 4742 ng/ml (48 h,  $P = 0.018$ ), and cTnI increased from 28.8 pg/ml (24 h) to 102 pg/ml (48 h,  $P = 0.017$ ). There was no significant change in CK-MB.

### Safety

In reviewing the complications, no haemothorax, pneumothorax, hepatic perforation, empyema, kink in the catheter, disconnection of the tubing, incisional infection or subcutaneous haematoma was

observed during or after the procedures. Although anticoagulation therapy was widely used in critically ill patients with COVID-19, there was no sign of haemorrhagic complications. No procedure-related infections were observed despite the wide use of glucocorticoids.

### Discussion

Scattered reports on pneumothorax and hydrothorax of COVID-19 have been published. Chen et al. reported that 1 out of 99 (1.0%) patients exhibited pneumothorax.<sup>1</sup> Yang et al. reported a similar incidence in deceased patients (1/91, 1.1%).<sup>4</sup> Yao et al.<sup>5</sup> and Zou et al.<sup>6</sup> found that pneumothorax developed after tracheal intubation in 5.9% and 5.4% of COVID-19 patients, respectively. Regarding hydrothorax, Mo et al. found that 10 out of 155 patients (6.5%) exhibited pleural effusion.<sup>7</sup> Feng et al. summarized that critical patients were far more susceptible to hydrothorax than moderate patients (18% v.s. 3.1%) after reviewing 476 patients.<sup>2</sup> We herein reported 11 critically ill patients who underwent pleural drainages. We studied their clinical characteristics, laboratory tests, changes in respiratory and circulatory indicators, details of the procedures and complications. To the best of our knowledge, this is the first study to report a series of critical patients with pleural drainages and evaluate the clinical outcomes.

Based on previous studies, evidence suggests that older males are more susceptible to SARS-CoV-2 infections<sup>8</sup> and more likely to need intubation.<sup>5</sup> Our data suggest that older males are also more susceptible to pneumothorax and hydrothorax. Of the enrolled patients, 7 (77.8%) were males, which is higher than the proportion in previous reports of critically ill patients (67%).<sup>9</sup> The mean age in our study

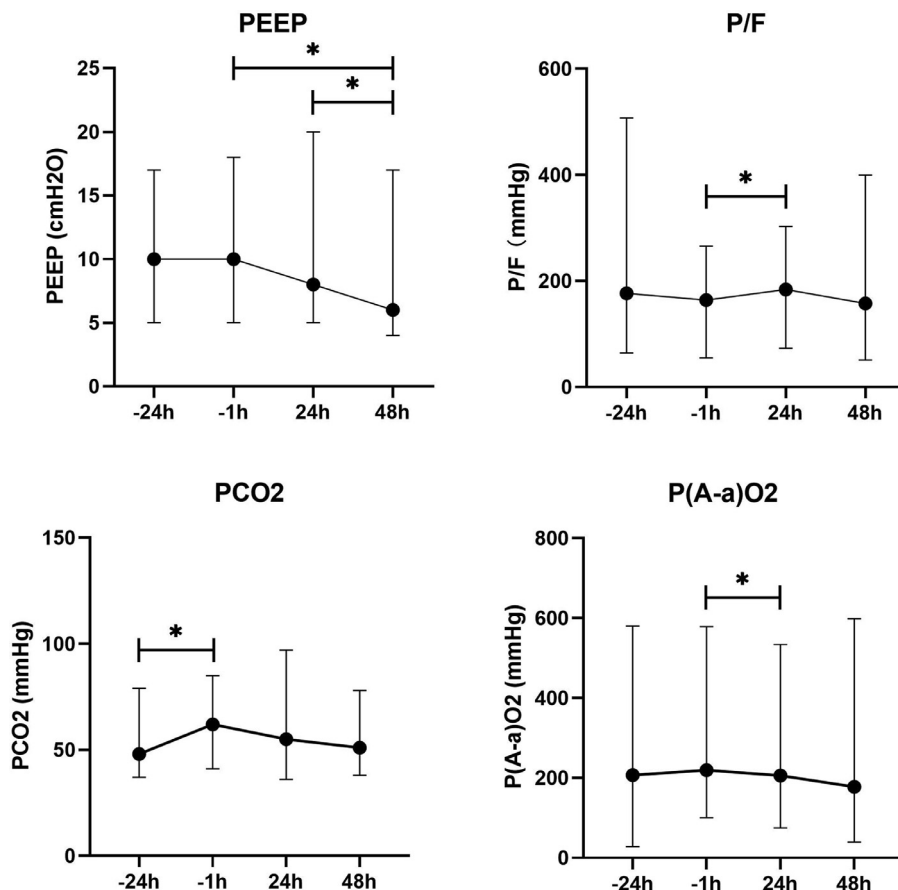


Fig. 2. Effect of pleural drainage on PEEP, the P/F ratio, PCO<sub>2</sub> and P(A-a)O<sub>2</sub>. \* $P < 0.05$ .

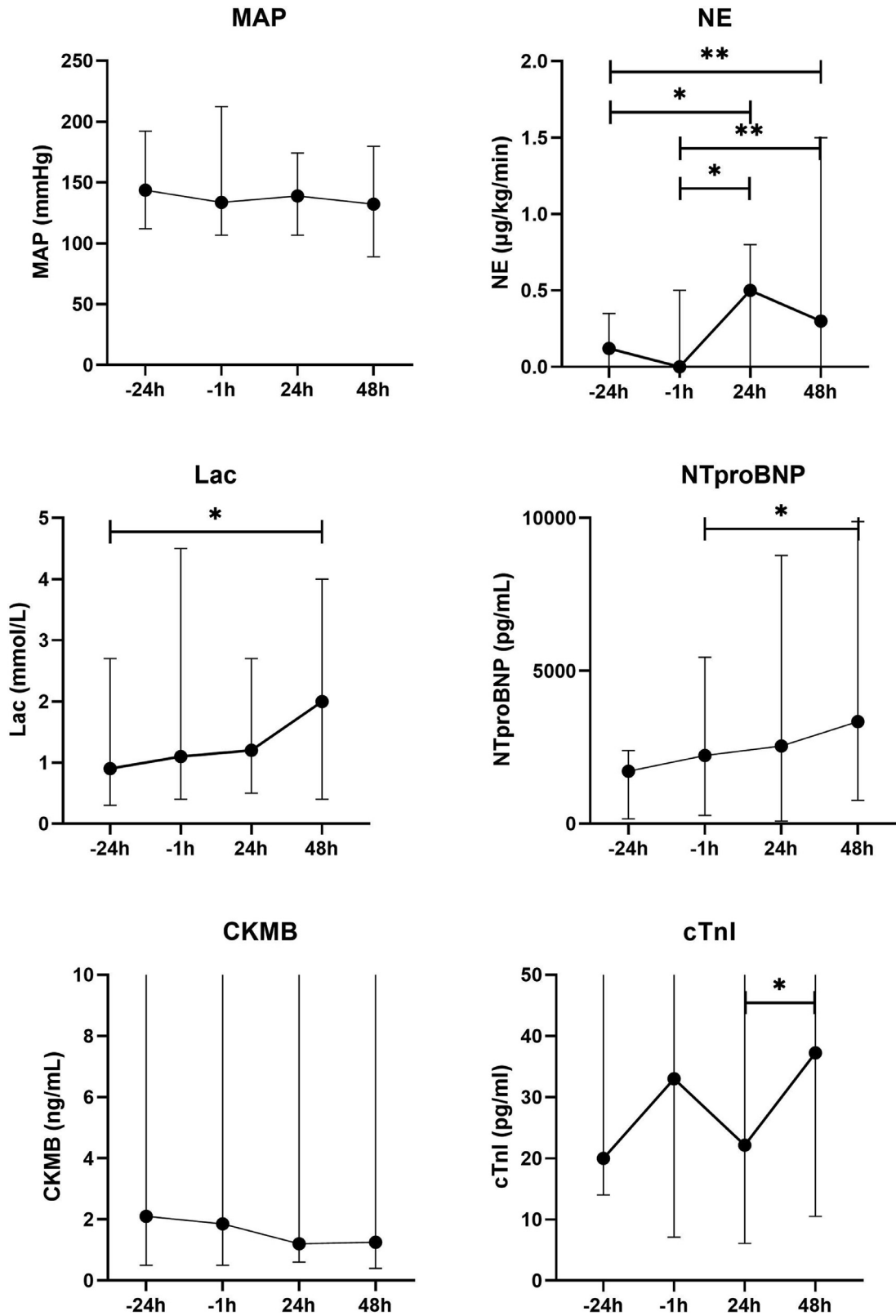


Fig.3. Effect of pleural drainage on MAP, noradrenaline (NE), lactate (Lac), NT-proBNP, CK-MB and cTnl. \*P < 0.05.

(67.2±7.9 years) was also higher than that in previous reports of critically ill patients (59.7±13.3 years).<sup>9</sup> Ayat et al. published a literature review and summarized 18 patients with COVID-19-associated pneumothorax. Eight of these patients were managed conservatively,

whereas 10 required chest tube insertion. Twelve patients had a favorable clinical course, whereas six patients passed away, resulting in a mortality rate of 33%.<sup>10</sup> It was inferred that pneumothorax and hydrothorax<sup>2</sup> might be predictive factors of poor prognosis. The



images also supported our hypothesis, as they showed crazy-paving patterns of consolidation and air bronchograms diffusely involved the bilateral lungs (Fig. 1).

Our study showed that pleural drainage benefitted the respiratory system by improving oxygenation and gas exchange. We observed a 19.1% improvement in the P/F ratio 24 h after the procedure, mirrored by a decrease in PEEP, which was maintained throughout the next 48 h (16.8% at 24 h and 24.3% at 48 h). This ongoing improvement could represent further drainage of fluid from the pleural space leading to greater lung re-expansion and recruitment of previously collapsed lung segments. Regarding gas exchange, we observed an increase in PCO<sub>2</sub> between -24 h and -1 h (9.5%), indicating a deterioration of gas exchange before the procedure. The mean PCO<sub>2</sub> decreased by 13.6% at 24 h and 21.4% at 48 h after the procedure, although no significant difference was observed. P(A-a)O<sub>2</sub> is another important indicator for gas exchange. It significantly decreased by 16.6% at 24 h. The improvements in oxygenation and gas exchange could also be observed in studies that explored the effects of pleural drainage on patients with mechanical ventilation and large pleural effusions. It was demonstrated that pleural drainage could increase the P/F ratio by 18%,<sup>11</sup> improve total thoracic volume<sup>12</sup> and improve lung compliance.<sup>13</sup> These findings suggested that areas of collapsed, poorly ventilated lung could re-expand after pleural drainage, thus improving V:Q matching in these areas and reducing arteriovenous shunting.

Circulatory indicators continued to deteriorate after pleural drainage. The increase in norepinephrine dosage and lactate suggested haemodynamic deterioration. As the changes in NT-proBNP, cTnI and CK-MB did not coordinate with each other, this deterioration was not unilaterally caused by heart dysfunction. There were two possible reasons for the inefficacy of pleural drainage to improve circulation. First, the drainage volume (average 1337 ml in 48 h) was not large enough to improve circulation. It was in accordance with Razazi's work, which did not show any improvement in hemodynamic variables of mechanically ventilated patients by removing >1000 mL of pleural effusion.<sup>14</sup> However, Wang et al. found a significant improvement in cardiac function with substantial improvement in diastolic function following the drainage of a >2000 mL pleural effusion.<sup>15</sup> Second, the slight improvement in circulation was inefficient to reverse the aggravation of primary disease, as 72.7% of the enrolled patients finally died.

To date, there has been no evidence to show that abnormalities in coagulation function or blood platelet count would add to haemorrhagic complications. Our study also showed that it was safe to perform pleural drainage while anticoagulation therapy was widely used. Therefore, as anticoagulation was necessary for the majority of critically ill patients with COVID-19, the limitations to APTT could be reduced. In our study, the APTT ranged from 42 to 70 s. However, a careful operation was highly necessary. For example, we should puncture close to the upper edge of the rib, as it might be difficult to stop the bleeding if the intercostal vessels are injured. Aseptic techniques should certainly be applied. Since neither thoracic nor incisional infections were observed in our study, we hypothesize it is safe to perform the procedure even though glucocorticoids are used. However, more data are needed to verify this.

The reason for developing pneumothorax and hydrothorax remains unclear. While pneumothorax is a well-known complication of mechanical ventilation, patients with high-flow nasal cannula (HFNC) oxygen therapy have also been reported to have pneumothorax.<sup>8, 16, 17</sup> Ashraf et al. also found a case with spontaneous pneumothorax which occurred 21 days after discharge.<sup>18</sup> These findings suggested that the primary disease (COVID-19) itself might also be a risk factor. Some authors suggested that pulmonary embolisms,<sup>16</sup> diffuse alveolar damage,<sup>16</sup> infections<sup>19</sup> might be the reasons. Underlying diseases of the lung might also be a risk factor, as patients in our study were older than critical patients reported elsewhere. Salah et al

suggested that complication induced cystic changes within the lung might be a reason.<sup>20</sup> Regarding hydrothorax, Light's criteria showed that all the effusions were exudate. These inflammatory exudates might be related to interstitial lung disease caused by COVID-19. This might explain why pleural effusion was rarely reported in mild patients, as pulmonary interstitial changes were not obvious at an early stage. Hypoproteinaemia caused by a negative nitrogen balance might also be an important factor, as this existed in 77.8% of the enrolled patients. In addition, cardiac dysfunction and kidney dysfunction might also be underlying reasons. Thoracic infection was not considered, as all the samples were negative in the cultures.

Large-bore chest tubes rather than CVCs are recommended, as 41.6% of CVCs were partially or fully obstructed while no chest tubes were obstructed. It would make sense that larger tubes would be expected to lead to better drainage. Concerns regarding safety and convenience might arise as catheters seem to be safer and easier to operate. However, for critically ill patients, unobstructed drainage should be the top priority. Liang et al. showed that pigtail catheters had prolonged durations of drainage, which may cause elevated infection rates (12%).<sup>11</sup> Our data also verified the safety of large-bore chest tubes.

Our study has several limitations. First, as it was a retrospective study, not all relevant clinical information was collected. For some patients, the laboratory tests were incomplete, making it difficult to report significant differences. Second, this was an observational study. As the respiratory and circulatory systems are influenced by multiple factors, case-control studies or even randomized controlled trials should be performed to further explore these factors. Third, only 11 patients were included. More data are needed to verify our results.

## Conclusion

Supportive therapy is widely regarded as the fundamental treatment for critically ill patients with COVID-19. For patients with pneumothorax and hydrothorax, our data support an active strategy for pleural drainage, as this procedure is safe and effective. Oxygenation and gas exchange significantly improved after drainage, but the deterioration of circulation was not reversed. It is safe to perform pleural drainage even though anticoagulation therapy and glucocorticoids are widely used. Large-bore chest tubes rather than CVCs are recommended. These data support further trials to confirm the ongoing effects of pleural drainage and to explore whether this procedure could reduce mortality.

## Author contributions

Dr. Shanqing li takes responsibility for the integrity of the data and the accuracy of the data analysis. He's also the guarantor of the paper.

Dr. Xu Yuan contributed to the design, overseeing and conduct of the study. He's the guarantor of the paper, taking responsibility for the integrity of the work as a whole.

Dr. Liu contributed to the study conception and design, analysis and interpretation of data, drafting of the manuscript, and revision of the manuscript.

## Data sharing

After publication, the data will be made available to others on reasonable requests to the corresponding author. A proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. Deidentified participant data will be provided after approval from the corresponding author and our hospital.

## Declaration of Competing Interest

The authors confirm that there are no conflicts of interest.

## Relevant acknowledgements

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