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Epidemiological and clinical characteristics of ammonia-producing microorganisms in the lungs of patients with severe pneumonia: a multicentre cohort study

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Abstract

Background *Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Mycoplasma hominis* were widely known as ammonia-producing microorganisms and can cause hyperammonemia, leading to cerebral edema and altered consciousness, which represent serious complications in lung transplant recipients. However, there is limited knowledge on the epidemiology and outcomes of infections caused by *U. urealyticum*, *U. parvum*, and *M. hominis* in non-transplant patients with severe pneumonia in the ICU.

Methods Patients with severe pneumonia who underwent clinical metagenomics of bronchoalveolar lavage fluid (BALF) at the intensive care units (ICUs) of 17 medical centers from January 2019 to March 2023 were enrolled. All cases were divided into the positive group and the negative group based on whether *U. urealyticum*, *U. parvum*, or *M. hominis* was detected in lower respiratory tract. The clinical characteristics and outcomes were compared among the groups. The survival analysis after propensity score matching (PSM) was used to evaluate whether the mortality rate of *U. urealyticum*, *U. parvum*, and *M. hominis* positive patients were increased. Multivariate logistic regression was used to evaluate whether these microbials positivity were a risk factor for central nervous system dysfunction.

Results In a total number of 1737 patients, 55 patients (3.17%) in the positive group and 1682 patients (96.83%) in the negative group. Patients in the positive group were younger, had a greater proportion of male patients, and had a longer time from ICU admission to clinical metagenomics testing. In contrast, the negative group had

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a higher proportion of patients with cerebrovascular disease. After PSM, there was no statistically significant difference in 28-day mortality following ICU admission between the two groups (hazard ratio [HR], 0.842; 95% confidence interval [CI], 0.489–1.451; p = 0.536). Multivariate logistic regression analysis showed an association between the detection of *U. urealyticum*, *U. parvum*, or *M. hominis* and neurological dysfunction (odds ratio [OR], 1.84; 95% CI 1.04–3.24; p = 0.035).

Conclusion The detection of *U. urealyticum*, *U. parvum*, or *M. hominis* in the lungs of patients is associated with neurological dysfunction.

Keywords *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma hominis*, Severe pneumonia, Hyperammonemia, Neurological dysfunction

Introduction

In the intensive care unit (ICU), various causes of consciousness disturbance exist, including global anoxic-ischemic injury, cerebrovascular disease (CVD), trauma, tumor, intracranial infection, autoimmune encephalitis, intoxications, Metabolic and endocrine disorder, among others [1, 2]. It is generally believed that elevated blood ammonia usually occurs in patients with acute liver failure or chronic liver disease. However, elevated blood ammonia levels may also occur in patients without underlying liver disease [3]. One such condition, hyperammonemia caused by infections from rare pathogens, is frequently overlooked such as *Ureaplasma urealyticum*, *Ureaplasma parvum*, and *Mycoplasma hominis* [4–9]. Although the detection of *U. urealyticum*, *U. parvum*, and *M. hominis* may lead to hyperammonemia in severe pneumonia, research in this area has primarily focused on lung transplant patients [4–9]. At present, no study reported the epidemiology and prognosis of ammonia-producing microbial infections in non-transplant lung infection patients in the ICU.

U. urealyticum, *U. parvum*, and *M. hominis* are fastidious organisms that are commonly found as part of the normal microbiome of the human urogenital tract [10]. The overgrowth of these microorganisms results in increased breakdown of urea and amino acids, reduced ammonia clearance, and consequently elevated serum ammonia levels. Previous studies have shown that the detection of *U. urealyticum, U. parvum,* and *M. hominis* (mainly from respiratory tract specimens) is associated with the development of serum ammonia levels [4, 5, 7, 11–13]. Early studies employed nucleic acid amplification testing or specialized culture methods for these microorganisms in bronchoalveolar lavage fluid (BALF) from patients with severe pneumonia, because they did not grow in routine bacteriological cultures [4]. Although a substantial amount of research indicates a correlation between hyperammonemia and pulmonary infections caused by *U. urealyticum*, *U. parvum*, and *M. hominis*, most of the relevant data comes from case reports, and more patients are likely being misdiagnosed [8, 12–15].

In this multicenter retrospective study, we report the clinical characteristics of patients with severe pneumonia who were positive for *U. urealyticum*, *U. parvum*, and *M. hominis* in the lungs, as well as their association with neurological dysfunction.

Methods

Study design

This was a multicenter, retrospective cohort study conducted in adult ICUs across 17 medical centers in China, between January 2019 and March 2023 as described before [16, 17]. The study was approved by the ethics committee of participating hospitals. The ethics committee waived the requirement for written informed consent for this retrospective study.

Patients' enrollment and definition

The inclusion criteria were patients with severe pneumonia in the ICU who underwent BALF clinical metagenomics. For those who underwent multiple BALF clinical metagenomics tests, only the first result was selected. The main exclusion criteria were: (1) Patients younger than 18 years old; (2) lost to follow-up within 28 days after admission to the ICU. In addition, we collected other clinical data including age, sex, underlying diseases, type of pneumonia, oxygen therapy methods, duration of mechanical ventilation, common laboratory test indicators, Sequential Organ Failure Assessment (SOFA) score on the day of clinical metagenomics testing, time from ICU admission to clinical metagenomics testing, as well as hospital stay, ICU stay, and prognosis within 28 days after ICU admission.

Severe pneumonia is defined by the presence of either one major criterion or three or more minor criteria [18]. The major criteria include: (1) septic shock with need for vasopressors; (2) respiratory failure requiring mechanical ventilation. The minor criteria include: (1) respiratory rate ≥ 30 breaths per minute; (2) PaO2/FiO2 ratio ≤ 250; (3) multilobar infiltrates; (4) confusion/disorientation; (5) uremia (blood urea nitrogen level > 20 mg/dl); (6) leukopenia (white blood cell count < 4,000 cells/μl);

(7) thrombocytopenia (platelet count < 100,000/μl); (8) hypothermia (core temperature < 36 °C); (9) hypotension requiring aggressive fluid resuscitation. Immunosuppression was defined as described before [19, 20]. Neurological dysfunction was defined as Glasgow Coma Scale was less than or equal to 12 points [21].

Clinical metagenomics

All clinical metagenomic tests adhered to the protocol previously reported and yielded results within 36 h post sample submission. During the clinical metagenomic examination, all patients or their family members were duly informed, and signed informed consent forms, in compliance with Chinese law, to authorize the procedure. If clinical metagenomics were performed multiple times, the results obtained from the initial instance were included in our analysis. The methodology employed for clinical metagenomics is detailed in the appendix.

Statistical methods

Continuous variables are presented as medians and interquartile ranges (median [Q1-Q3]), while categorical variables are presented as percentages. Statistical significance was assessed using Kruskal–Wallis for continuous variables and the $\chi 2$ or Fisher's exact test for categorical variables. Propensity score matching analysis was performed using a 1:2 optimal matching method and a caliper width of 0.02, using the "MatchIt" package in R software, to establish balance in baseline characteristics between the positive and negative groups. In the matched cohort, Kaplan–Meier survival analysis was employed to compare the 28-day mortality between the two groups after ICU admission. Furthermore, to determine if the detection of *U. urealyticum*, *U. parvum*, or *M. hominis* is an independent risk factor for poor neurological function, we conducted a multivariate regression analysis. The variables encompassed in the study were age, sex, clinical metagenomics test positivity, the other five SOFA scores apart from neurological function, a history of transplantation and CVD, type of pneumonia, and respiratory support, all of which were identified in previous research. We used cardiovascular dysfunction to replace severe hemodynamic disturbances, and respiratory support to replace the use of analgesia and sedation. All statistical analyses and plotting were performed using R software (v4.4.0), and $p < 0.05$ (two-tailed) was considered significant. If data were missing by more than 10%, they were excluded; otherwise, multiple imputation methods were used for estimation.

Sensitive analysis

Sensitivity analyses were performed using logistic regression to evaluate whether ammonia-producing microorganisms are associated with neurological dysfunction. First, we excluded all patients with a history of transplantation to determine the association between ammonia-producing microorganisms and neurological dysfunction because the previous studies of these three microorganisms were limited to transplant patients. Second, we excluded all patients with CVD to reduce the impact of this comorbidity, which was most associated with neurological dysfunction. Finally, we excluded both comorbidities and performed additional sensitivity analyses.

Results

A total of 1737 patients with severe pneumonia were enrolled (Fig. 1). Among them, 55 patients tested positive for *U. urealyticum*, *U. parvum*, or *M. hominis* in the lungs, defined as the positive group (3.17%); while 1682 patients who tested negative for *U. urealyticum*, *U. parvum*, or *M. hominis* were defined as the negative group (96.83%).

Patients in the positive group were younger (56 vs. 67, $p < 0.001$), the proportion of male patients was greater (89.1% vs 69.4%, $p = 0.003$), and the time from ICU admission to clinical metagenomics testing was longer (3 vs. 5, $p = 0.015$) (Table 1). In contrast, the negative group had a higher proportion of patients with CVD (16.4% vs 5.5%, $p = 0.047$). There was no significant difference in the proportion of organ transplants between the two groups (10.9% vs 4.9%, $p = 0.090$).

The main clinical manifestations in the positive group were coma in 21 patients, drowsiness in 7 patients, and epilepsy in 2 patients, with the highest proportion of coma occurring in the *U. parvum* group at 52.9% (Table 2). In addition, 23.5% of the *U. urealyticum* group had a history of kidney transplantation, and 15.8% of the U. parvum group had undergone lung transplantation. Prior to clinical metagenomics testing, 8 patients received Quinolones and 1 patient received Macrolides. Among 55 patients, 13 underwent blood ammonia level measurement, with the highest levels found in the group containing at least two pathogens, while the lowest levels were observed in the *U. parvum* group. CT scans showed that the group with the highest proportion of cerebral edema was the *U. parvum* group, accounting for 64.3%, while the median intracranial pressure in the positive group was 250 cmH_2O. A total of 19 patients (34.5%) received medication treatment, with Quinolones administered to 12 patients, Tetracyclines to 4, and Macrolides to 3. The effective rates of treatment were 40% for the *U. urealyticum* group, 60% for the *U. parvum* group, 50% for the *M. hominis* group, and 80% for those with at least two pathogens.

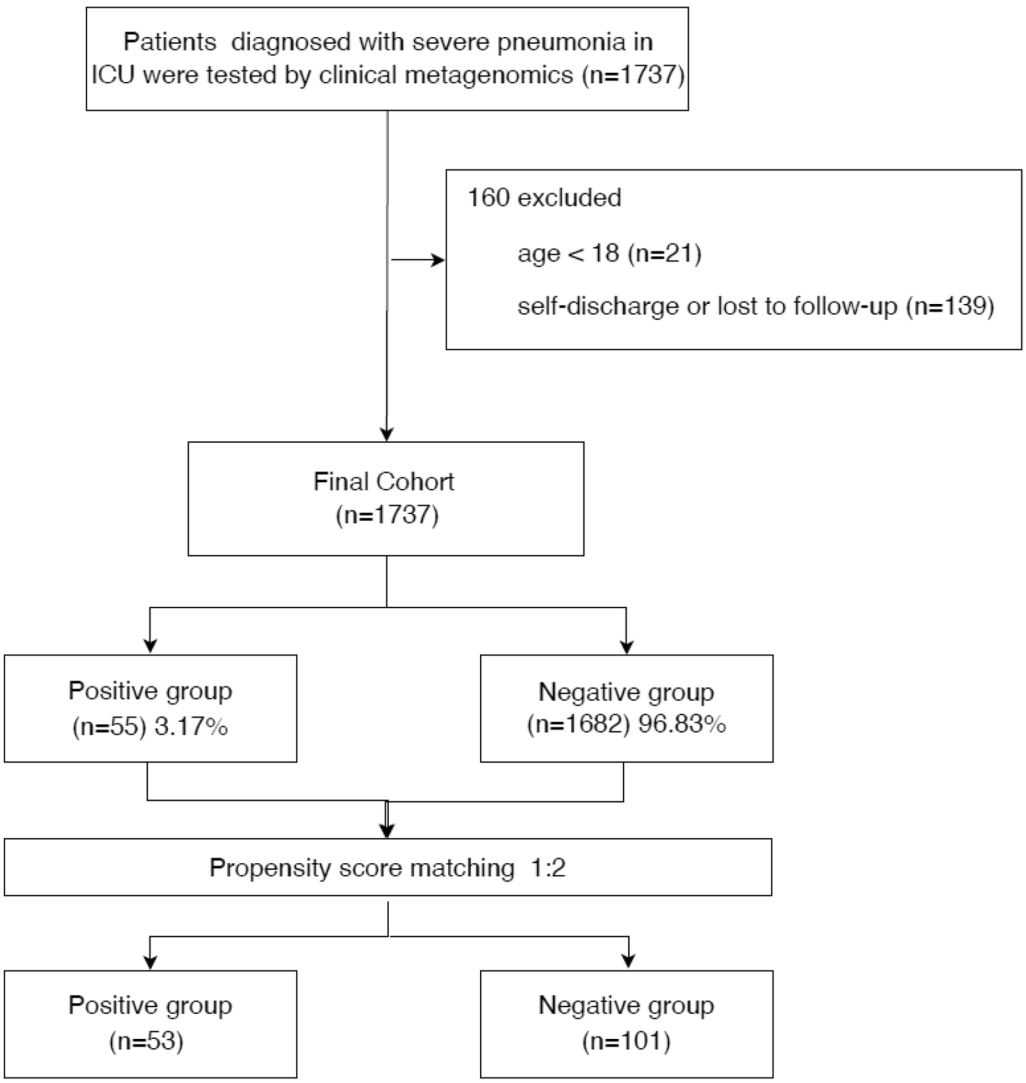

Fig. 1 Flowchart of the patients

When we included historical variables that were associated with neurological dysfunction in multivariable logistic regression analysis, the presence of *U. urealyticum*, *U. parvum*, or *M. hominis* was an independent risk factor for neurological dysfunction (OR, 1.84; 95% CI 1.04–3.24; p = 0.035) (Fig. 2). Additionally, CVD, thrombocytopenia, cardiovascular dysfunction, VAP were associated with neurological dysfunction in patients with severe pneumonia.

After balancing age, sex, SOFA score at clinical metagenomics testing, CVD, type of pneumonia, and time from ICU admission to clinical metagenomics through PSM, there were no differences in baseline characteristics between the two groups (Table 1 and Figure S1). Besides, we found that there were no statistics differences about the 28-day mortality rate in the positive group and in the negative group (35.8% vs 40.6%, p = 0.689). Kaplan–Meier survival curve analysis showed no statistical difference in mortality between the two groups (HR, 0.842; 95% CI 0.489–1.451; p = 0.536) (Fig. 3).

Subsequent sensitivity analyses showed that in patients without transplantation (OR, 1.80; 95% CI 0.99–3.25; p = 0.052), patients without CVD (OR, 1.97; 95% CI 1.10–3.52; p = 0.022), and patients without both transplantation and CVD (OR, 1.98; 95% CI 1.08–3.65; p = 0.028), OR was greater than 1. (Figures S2–S4).

Table 1 Characteristics of ICU patients with or without *U. urealyticum*, *U. parvum*, and *M. hominis* positivity

Variables	Before PSM			After PSM		
	Positive group (n = 55)	Negative group (n = 1682)	P-value	Positive group (n = 53)	Negative group (n = 101)	P-value
Age, median (IQR)	56 (45,68)	67 (56,75)	< 0.001	56 (48,68)	58.0 (41,71)	0.923
Male, n (%)	49 (89.1)	1167 (69.4)	0.003	47 (88.7)	86 (85.1)	0.719
Comorbidities, n (%)						
Diabetes mellitus	13 (23.6)	414 (24.6)	0.995	13 (24.5)	20 (19.8)	0.637
MI	2 (3.6)	101 (6.0)	0.659	2 (3.8)	5 (5.0)	1.000
COPD	7 (12.7)	343 (20.4)	0.221	7 (13.2)	18 (17.8)	0.612
Liver disease	4 (7.3)	114 (6.8)	1.000	4 (7.5)	6 (5.9)	0.968
Chronic renal disease	9 (16.4)	210 (12.5)	0.518	9 (17.0)	13 (12.9)	0.653
Solid tumor	4 (7.3)	257 (15.3)	0.149	4 (7.5)	17 (16.8)	0.178
Hematologic neoplasms	0 (0.0)	91 (5.4)	0.143	0 (0.0)	4 (4.0)	0.350
Immunosuppression	14 (25.5)	416 (24.7)	1.000	14 (26.4)	29 (28.7)	0.910
CTD	1 (1.8)	73 (4.3)	0.567	1 (1.9)	3 (3.0)	1.000
CVD	3 (5.5)	276 (16.4)	0.047	3 (5.7)	4 (4.0)	0.941
Transplantation	6 (10.9)	82 (4.9)	0.090	6 (11.3)	12 (11.9)	1.000
Type of pneumonia, n (%)			0.057			0.699
CAP	25 (45.5)	1026 (61.0)		25 (47.2)	51 (50.5)	
HAP	17 (30.9)	402 (23.9)		17 (32.1)	26 (25.7)	
VAP	13 (23.6)	254 (15.1)		11 (20.8)	24 (23.8)	
Respiratory support, n (%)			0.841			0.459
IMV	49 (89.1)	1461 (86.9)		47 (88.7)	92 (91.1)	
NIV	1 (1.8)	51 (3.0)		1 (1.9)	4 (4.0)	
Other	5 (9.1)	170 (10.1)		5 (9.4)	5 (5.0)	
Duration of IMV, median (IQR)	8.0 (4.0,15.0)	8.0 (3.0,16.0)	0.897	8.0 (4.0,15.0)	10.0 (4.0,19.0)	0.239
Laboratory tests, median (IQR)						
White blood cell	10.7 (7.8,15.7)	11.1 (6.9,15.7)	0.795	10.6 (7.7,15.3)	10.3 (7.3,15.2)	0.926
Lymphocyte	0.6 (0.3,1.2)	0.6 (0.3,1.0)	0.991	0.6 (0.3,1.1)	0.5 (0.3,1.0)	0.866
Neutrophil	9.2 (6.5,13.5)	9.5 (5.6,14.1)	0.859	8.9 (6.4,13.3)	9.1 (4.6,13.9)	0.938
CRP	75.0 (23.7,120.1)	88.9 (31.1,160.9)	0.183	74.9 (18.5,119.1)	89.2 (25.1,148.1)	0.277
PCT	1.1 (0.3,7.7)	0.9 (0.2,5.3)	0.659	1.1 (0.3,7.3)	1.2 (0.3,7.9)	0.683
SOFA at clinical metagenomics testing, median (IQR)	8.0 (5.0,12.0)	7.0 (5.0,10.0)	0.329	8.0 (5.0,12.0)	8.0 (5.0,10.0)	0.707
Organ dysfunction, n (%)[a]						
Respiration	46 (83.6)	1420 (84.4)	1.000	44 (83.0)	82 (81.2)	0.952
Coagulation	18 (32.7)	611 (36.3)	0.686	18 (34.0)	41 (40.6)	0.529
Liver	9 (16.4)	268 (15.9)	1.000	8 (15.1)	23 (22.8)	0.359
Cardiovascular	27 (49.1)	840 (49.9)	1.000	26 (49.1)	48 (47.5)	0.991
Central nervous system	26 (47.3)	610 (36.3)	0.127	26 (49.1)	41 (40.6)	0.404
Renal	17 (30.9)	374 (22.2)	0.177	16 (30.2)	21 (20.8)	0.272
Time from ICU admission to clinical metagenomics, median (IQR)	3.0 (2.0,7.0)	5.0 (3.0,9.5)	0.015	5.0 (3.0,9.0)	4.0 (2.0,9.0)	0.5
Hospital LOS, median (IQR)	21.0 (12.0,35.0)	25.0 (10.0,49.5)	0.347	24.0 (10.0,47.0)	24.0 (15.0,40.0)	0.822
ICU LOS, median (IQR)	13.0 (7.0,23.0)	13.0 (8.0,23.5)	0.947	12.0 (8.0,20.0)	14.0 (7.0,24.0)	0.479
28 day-mortality, n (%)	19 (34.5)	699 (41.6)	0.368	19 (35.8)	41 (40.6)	0.689

[a] Organ dysfunctions were defined as a SOFA score of 2 or higher for each of 6 components

ICU intensive care unit, *IQR* interquartile range, *MI* myocardial infarction, *COPD* chronic obstructive pulmonary disease, *CTD* connective tissue disease, *CVD* cerebrovascular disease, *CAP* community-acquired pneumonia, *HAP* hospital acquired pneumonia, *VAP* ventilator associated pneumonia, *IMV* invasive mechanical ventilation, *NIV* non-invasive mechanical ventilation, *CRP* C-reactive protein, *PCT* procalcitonin, *SOFA* sequential organ failure assessment, *LOS* length of stay

Table 2 Characteristics of the patients with *U. urealyticum*, *U. parvum*, and *M. hominis* positivity

	Ureaplasma urealyticum (n = 17)	Ureaplasma parvum (n = 19)	Mycoplasma hominis (n = 13)	≥ two pathogens (n = 6)
Clinical symptoms, n (%)				
Drowsiness	2 (11.8)	2 (10.5)	1 (7.7)	2 (33.3)
Coma	5 (29.4)	10 (52.6)	4 (30.8)	2 (33.3)
Epilepsy	0 (0)	2 (10.5)	0 (0)	0 (0)
History of transplantation, n (%)				
Kidney	4 (23.5)	0(0)	0(0)	1 (16.7)
Lung	0 (0)	3 (15.8)	1 (7.7)	0 (0)
Antimicrobial treatment before clinical metagenomics testing, n (%)				
Macrolides	1 (5.9)	0 (0)	0 (0)	0 (0)
Quinolones	2 (11.8)	4 (21.1)	1 (7.7)	1 (16.7)
Blood ammonia test, n (%)	4 (23.5)	4 (21.1)	4 (30.8)	1 (16.7)
Blood ammonia, median (IQR)	69.5 (38.2, 132.2)	22.5 (10.2, 34.2)	36.8 (30.9, 39.0)	432.0
Head CT scan, n (%)	11 (64.7)	14 (73.7)	9 (69.2)	5 (83.3)
Cerebral edema	2 (18.2)	9 (64.3)	3 (33.3)	1 (20.0)
Lumbar puncture, n (%)	1 (5.9)	3 (15.8)	2 (15.4)	3 (50.0)
Intracranial pressure, cm H2O, median (IQR)	270.0	170.0 (127.5,310.0)	250.0 (250.0,250.0)	200.0 (150.0,240.0)
Therapeutic drug, n (%)				
Macrolides	1 (5.9)	0(0)	0(0)	2 (33.3)
Quinolones	2 (11.8)	4 (21.1)	3 (23.1)	3 (50.0)
Tetracyclines	2 (11.8)	1 (5.3)	1 (7.7)	0(0)
Improvement in patients with treatment, n (%)	2 (40.0)	3 (60.0)	2 (50.0)	4 (80.0)

SD standard deviation, *CT* computed tomography

Discussion

Researches on ammonia-producing microorganisms was primarily confined to lung transplant recipients [4]. However, the prevalence and clinical features in non-transplant patients remain poorly understood, and there has been a lack of extensive studies in this area. This study is the first to report an association between age, sex, and time of ICU admission and the detection of ammonia-producing microorganisms. Our research found that patients in the group with detected ammonia-producing microorganisms were younger, though the specific reasons remain unclear.

U. urealyticum, *U. parvum*, and *M. hominis* are commonly commensal organisms in the human urogenital tract. Because they do not grow in standard bacterial cultures, they are rarely identified. *U. urealyticum* is a microorganism from the Mycoplasma genus, lacking a cell wall, and is one of the smallest prokaryotic microorganisms. *U. parvum* is related to *U. urealyticum*, but it is not the same species. In some studies, it has been classified as a subspecies of Ureaplasma urealyticum. *M. hominis* is similar to Ureaplasma in lacking a cell wall, and it can grow on standard blood agar plates, with its colonies exhibiting a unique "fried egg" appearance. Ammonia is the result of its metabolic process, generated through urea hydrolysis for energy production. In immunosuppressed patients, invasive infections caused by ammonia-producing microorganisms lead to HS [22, 23].

There is a notable association between ammonia-producing microorganisms and lung transplant recipients, though the underlying cause remains unclear. One hypothesis suggests a deficiency in glutamine synthetase may play a role [24]. In this study, the detection of ammonia-producing microorganisms in non-lung transplant patients did not result in a statistically significant difference in 28-day mortality compared to the negative group. However, in lung transplant patients, their presence is associated with increased mortality [25]. Key factors related to the detection of these microorganisms in lung transplant patients include donor age, purulent secretions observed during donor bronchoscopy, prolonged mechanical ventilation, the need for blood purification therapy, and extended ICU stays [6].

This study suggests an association between ammonia-producing microorganisms and neurological dysfunction in patients, though a direct causal relationship remains

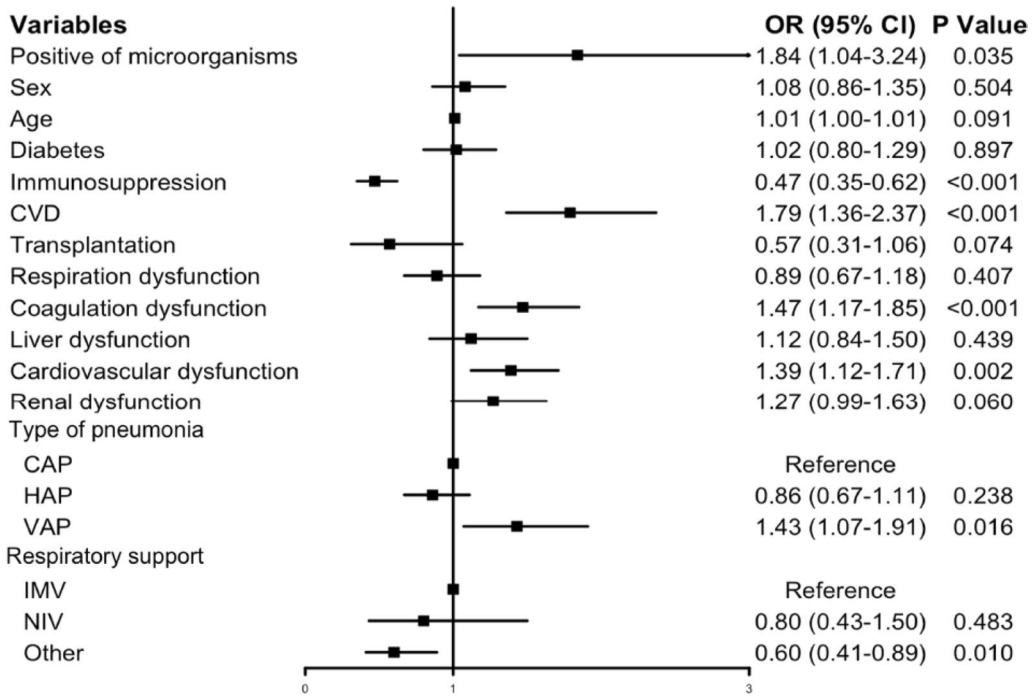

Fig. 2 Multivariate logistic regression analysis of risk factors for neurological dysfunction. *OR* odds ratio, *CI* confidence interval, *CVD* cerebrovascular disease, *CAP* community-acquired pneumonia, *HAP* hospital acquired pneumonia, *VAP* ventilator-associated pneumonia, *IMV* invasive mechanical ventilation, *NIV* non-invasive ventilation

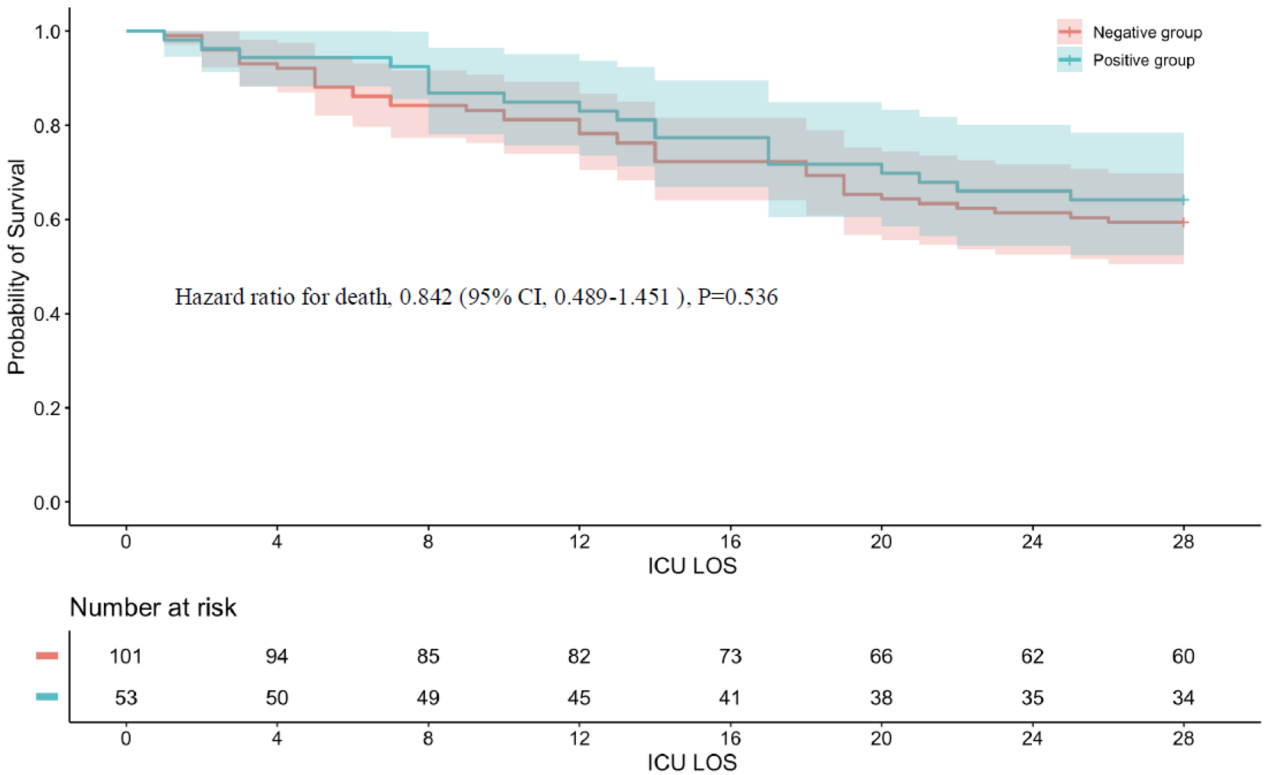

Fig. 3 Kaplan–Meier survival curves of patients in the positive group (pale green) and in the negative group (pink). *ICU* intensive care unit, *LOS* length of stay, *CI* confidence interval

uncertain. Although only 9 patients underwent lumbar puncture, most of the cerebrospinal fluid pressure was significantly elevated, and 15 (38.5%) patients demonstrated cerebral edema on CT scans, which could have contributed to the observed neurological dysfunction. These microorganisms are typically undetectable through routine bacterial culture. Even when clinical metagenomics identifies ammonia-producing microorganisms, most clinicians do not measure blood ammonia levels, indicating that the potential role of these microorganisms in central nervous system disorders may be underestimated. Dal-Pizzol et al. reported that minocycline could reduce the incidence of delirium and mortality in critically ill patients [26], though it is unclear whether this effect is due to the antibiotic's action on Ureaplasma or its decolonization [27]. It remains undetermined whether ammonia-producing microorganisms act as colonizers or pathogens, and whether patients with positive findings of these microorganisms in the lungs should be routinely treated with antibiotics warrants further investigation. Many microorganisms detected by clinical metagenomics are not regarded as causative pathogens of infection. However, numerous colonizing microorganisms may still exert biological effects [17].

This study suggests an association between the detection of *U. urealyticum*, *U. parvum*, or *M. hominis* and neurological dysfunction in patients with severe pneumonia. Similarly, in the sensitivity analysis in patient without a history of CVD and in those without both CVD and transplantation, we also reached the same conclusion. However, the causal relationship between these factors remains unclear. Although other conditions such as encephalitis, hypoglycemia, hyperglycemia, and electrolyte disorders can also impact neurological dysfunction, these are relatively easier for ICU physicians to detect and manage. Therefore, future randomized controlled trials are necessary to determine whether routine screening for ammonia-producing microorganisms, along with decolonization or anti-infective treatments, is warranted in critically ill patients.

Our study has several limitations. First, as a retrospective study, it is subject to potential biases and includes some missing data. Additionally, we were unable to establish a causal relationship between ammonia-producing microorganisms and neurological dysfunction. Second, quantitative PCR for ammonia-producing microorganisms was not conducted, and further prospective studies are needed to clarify the impact of these microorganisms on neurological dysfunction. Third, it is indeed challenging to differentiate whether the presence of *U. urealyticum*, *U. parvum*, and *M. hominis* is indicative of infection or simply colonization. Finally, there is a lot of missing data on blood ammonia testing, due to the lack of understanding among clinical doctors about the relationship between ammonia-producing microorganisms and neurological dysfunction. However, the lack of routine testing for blood ammonia may reflect limited awareness among clinicians regarding this condition.

Conclusions

U. urealyticum, *U. parvum*, or *M. hominis* were detected in the lungs of 3.17% patients with severe pneumonia. The detection of *U. urealyticum*, *U. parvum*, or *M. hominis* in the lungs of patients with severe pneumonia is associated with neurological dysfunction.

Abbreviations

ICU	Intensive care unit
CT	Computed tomography
SOFA	Sequential organ failure assessment
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio
BAL	Broncho-alveolar lavage
CHD	Coronary atherosclerotic heart disease
COPD	Chronic obstructive pulmonary disease
CKD	Chronic kidney disease
CTD	Connective tissue disease
CVD	Cerebrovascular disease
CAP	Community-acquired pneumonia
HAP	Hospital acquired pneumonia
VAP	Ventilator-associated pneumonia
IMV	Invasive mechanical ventilation
NIV	Non-invasive ventilation
PCT	Procalcitonin
CRP	C-reactive protein
LOS	Length of stay

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-024-05974-2.

Supplementary material 1: Figure S1. Summaries of variables before and after propensity score matching. Figure S2. Multivariate logistic regression analysis of risk factors for neurological dysfunction in patients without transplantation. Figure S3. Multivariate logistic regression analysis of risk factors for neurological dysfunction in patients without CVD. Figure S4. Multivariate logistic regression analysis of risk factors for neurological dysfunction in patients without both CVD or transplantation.

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Author contributions

HLC, LTH, HZS, QX designed the study and reviewed the final manuscript; JX, XDR, XHH, YJ analyzed the data and wrote the manuscript; MQW, LZ, GJH, SFW, QQW, MHD, YHX, YHX, XWH, YJP, HYW participated in data collection and collation. All investigators participated in the discussion and agreed with the final version of the manuscript.

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Availability of data and materials
The data can be obtained from the corresponding author Hongliu Cai (1193001@zju.edu.cn) upon reasonable request.

Declarations

Ethics approval and consent to participate
The study has been approved by the ethics committees of the first affiliated hospital, Zhejiang university school of medicine and other participating hospitals. As a retrospective study, informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Sakusic A, Rabinstein AA. Acute coma. Neurol Clin. 2021;39:257–72.
2. Edlow JA, Rabinstein A, Traub SJ, Wijdicks EFM. Diagnosis of reversible causes of coma. Lancet. 2014;384:2064–76.
3. Watson AJ, Chambers T, Karp JE, Risch VR, Walker WG, Brusilow SW. Transient idiopathic hyperammonaemia in adults. Lancet. 1985;2:1271–4.
4. Buzo BF, Preiksaitis JK, Halloran K, Nagendran J, Townsend DR, Zelyas N, et al. Association between mycoplasma and ureaplasma airway positivity, ammonia levels, and outcomes post-lung transplantation: a prospective surveillance study. Am J Transpl. 2021;21:2123–31.
5. Wylam ME, Kennedy CC, Hernandez NM, Peters SG, Maleszewski JJ, Cassivi SD, et al. Fatal hyperammonaemia caused by mycoplasma hominis. Lancet. 2013;382:1956.
6. Tam PCK, Hardie R, Alexander BD, Yarrington ME, Lee MJ, Polage CR, et al. Risk factors, management, and clinical outcomes of invasive mycoplasma and ureaplasma infections after lung transplantation. Am J Transpl. 2024;24:641–52.
7. Bharat A, Scott Budinger GR, Ison MG. Donor-derived ureaplasma is a potentially lethal infection in lung allograft recipients. J Heart Lung Transpl. 2017;36:917–8.
8. Paparoupa M, Barten MJ, de Heer J, Giessen HS, Frings D, Kluge S. Hyperammonemia by ureaplasma urealyticum pneumonia after lung transplantation. Respir Med Case Rep. 2020;30:101080.
9. Fernandez R, Ratliff A, Crabb D, Waites KB, Bharat A. Ureaplasma transmitted from donor lungs is pathogenic after lung transplantation. Ann Thorac Surg. 2017;103:670–1.
10. Bharat A, Cunningham SA, Scott Budinger GR, Kreisel D, DeWet CJ, Gelman AE, et al. Disseminated ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med. 2015;7:284re3.
11. Roberts SC, Bharat A, Kurihara C, Tomic R, Ison MG. Impact of screening and treatment of ureaplasma species on hyperammonemia syndrome in lung transplant recipients: a single center experience. Clin Infect Dis. 2021;73:e2531–7.
12. Farfour E, Vasse M, Vallée A. Mollicutes-related infections in thoracic surgery including lung and heart transplantation: a systematic review. J Heart Lung Transpl. 2024;43:169–80.
13. Buzo BF, Preiksaitis JK, Halloran K, Nagendran J, Townsend DR, Zelyas N, et al. Hyperammonemia syndrome post-lung transplantation: case series and systematic review of literature. Transpl Infect Dis. 2022;24: e13940.
14. Bharath SP, Pang H, Kaderi T, Rampolla R, Chen T, Gezalian M, et al. Pearls & oy-sters: Status epilepticus and cerebral edema from hyperammonemia due to disseminated ureaplasma and mycoplasma species. Neurology. 2023;100:727–31.
15. Bächle F, Bansbach J, Hettich I, Lambeck J, Senbaklavaci Ö, Kalbhenn J. Posterior reversible encephalopathy syndrome and hyperammonemia: two entities causing cerebral edema and status epilepticus in a female patient after lung transplantation. Anaesthesist. 2020;69:506–13.
16. Wei X, Huang X, Gu S, Cai H, Wang M, Wang H, et al. Landscape of fungal detection in the lungs of patients with severe pneumonia in the ICU, a multicenter study based on clinical metagenomics. J Infect. 2024;89:106195.
17. Jiang Y, Huang X, Zhou H, Wang M, Wang S, Ren X, et al. Clinical characteristics and prognosis of patients with severe pneumonia with pneumocystis jirovecii colonization: a multicenter, retrospective study. Chest. 2024;S0012–3692(24):04841–4.
18. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infectious diseases society of America. Am J Respir Crit Care Med. 2019;200:e45-67.
19. Xu J, Zhong L, Shao H, Wang Q, Dai M, Shen P, et al. Incidence and clinical features of HHV-7 detection in lower respiratory tract in patients with severe pneumonia: a multicenter, retrospective study. Crit Care. 2023;27:248.
20. Huang L, Zhang X, Pang L, Sheng P, Wang Y, Yang F, et al. Viral reactivation in the lungs of patients with severe pneumonia is associated with increased mortality, a multicenter, retrospective study. J Med Virol. 2023;95: e28337.
21. Liu S, Yao C, Xie J, Liu H, Wang H, Lin Z, et al. Effect of an herbal-based injection on 28-day mortality in patients with sepsis: the EXIT-SEP Randomized clinical trial. JAMA Intern Med. 2023;183:647–55.
22. Ranganath N, Issa NS, Rosenbaum AN, Beam E, Mahmood M. Use of novel diagnostic approaches to identify disseminated ureaplasma urealyticum infection causing hyperammonemia syndrome after heart-kidney transplant. Mayo Clin Proc. 2023;98:804–6.
23. Smith M, Crews JD, Cheek N, Srivastava R, Appachi E. Hyperammonemic encephalopathy due to ureaplasma parvum infection in an immunocompromised child. Pediatrics. 2019;144: e20190601.
24. Tuchman M, Lichtenstein GR, Rajagopal BS, McCann MT, Furth EE, Bavaria J, et al. Hepatic glutamine synthetase deficiency in fatal hyperammonemia after lung transplantation. Ann Intern Med. 1997;127:446–9.
25. Chen C, Bain KB, Iuppa JA, Yusen RD, Byers DE, Patterson GA, et al. Hyperammonemia syndrome after lung transplantation: a single center experience. Transplantation. 2016;100:678–84.
26. Dal-Pizzol F, Coelho A, Simon CS, Michels M, Corneo E, Jeremias A, et al. Prophylactic minocycline for delirium in critically ill patients: a randomized controlled trial. Chest. 2024;165:1129–38.
27. Wang C, Wang J, Yan J, Chen F, Zhang Y, Hu X. Mycoplasma hominis, ureaplasma parvum, and ureaplasma urealyticum: hidden pathogens in peritoneal dialysis-associated peritonitis. Int J Infect Dis. 2023;131:13–5.

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