Clinical Characteristics of Pneumonia in Chinese Hemodialysis Patients

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To the editor: Patients undergoing maintenance hemodialysis (MHD) are more vulnerable to nosocomial infection, with less ability to combat the infection and a greater susceptibility to contaminants in the dialysis environment. Infection is a frequent cause of hospitalization, second only to cardiovascular disease (CVD) as the leading cause of death in dialysis patients. Data from the United States Renal Data System indicated that 27.9% of MHD patients were diagnosed with pneumonia during their 1st year of hemodialysis (HD). At present, in China, hospital-based HD facilities are fully occupied, with HD patients accounting for 86% of the dialysis population. Surprisingly, increasing pneumonia-related morbidity and mortality rates among MHD patients has received little attention, which is confirmed by our PubMed search results (45 citations, August 31, 2017).

Therefore, we have conducted this study to further explore the following issues among MHD patients: (a) the incidence and risk factors of the first hospitalization with pneumonia, (b) cumulative pneumonia-free and overall survival, and (c) the microbial spectrum of pneumonia.

A single-center retrospective cohort study was conducted in strict compliance with the Strengthening the Reporting of Observational Studies in Epidemiology checklists. Data for this retrospective cohort study analysis were collected from patients who had undergone regular MHD for at least three months at our HD center, between March 1, 2013 and August 31, 2017. Patients were excluded if they were: (a) younger than 18-year-old, (b) pregnant, (c) diagnosed with carcinoma, or (d) under infectious status they were: (a) younger than 18-year-old, (b) pregnant, (c) diagnosed with carcinoma, or (d) under infectious status.

Primary outcomes included first pneumonia hospitalization and mortality after 3 months of MHD. First pneumonia hospitalization was identified according to discharge diagnosis, and double-checked by the personnel through screening the results of laboratory test and chest computed tomography scan, given that pulmonary edema commonly occurs in MHD patients. Follow-up of the patients was censored at time of death, kidney transplantation, patient withdrawal, or transfer to a nonparticipating hospital.

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Baseline characteristics were compared across two groups, characterized as with or without pneumonia during follow-up. Continuous variables that fit the normal distribution assumptions were presented as mean ± standard deviation (SD) and analyzed by independent sample t-test, while variables with skewed distributions were expressed as medians accompanied by interquartile range and analyzed using the Mann–Whitney test. Pearson’s Chi-square test or Fisher’s exact test was used to determine if there were differences in the levels of categorical variables between these two groups. Survival curves were estimated by the Kaplan–Meier method for first pneumonia-related hospitalization after 3-month MHD and all-cause mortality. A Cox proportional hazards regression model was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the two outcomes. A two-sided \( P < 0.05 \) was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics Version 22.0 (Chicago, IL, USA).

Through August 31, 2017, 267 patients were included in this cohort, with 253 MHD patients finally enrolled (205 and 48 participants, respectively, in the groups without and with pneumonia-related hospitalization). The baseline characteristics of the participants are listed in Table 1. The overall median age of the patients in the final cohort was 50 years old; 58.9% of these patients were male and 21.3% of them had DM. Patients in the pneumonia group were older, with a higher proportion of females, a lower URR, a higher proportion of comorbidities including DM, HTN, and HF, and lower levels of serum ALB.

### Table 1: Baseline characteristics of study patients undergoing hemodialysis in the hemodialysis center

| Characteristics | All (n = 253) | Nonpneumonia (n = 205) | Pneumonia (n = 48) | P* |
|----------------|--------------|------------------------|-------------------|----|
| Age (years)    | 50.0 (40.5, 65.0) | 48.0 (39.0, 62.0) | 62.5 (46.0, 71.0) | <0.001 |
| Gender         |              |                        |                   |    |
| Male, n (%)    | 149 (58.9) | 127 (62.0) | 22 (45.8) | 0.041 |
| Smoker, n (%)  | 108 (42.7) | 95 (46.3) | 13 (27.1) | 0.016 |
| Alcohol consumption, n (%) | 100 (39.5) | 89 (43.4) | 11 (22.9) | 0.009 |
| Education (less than high school), n (%) | 145 (56.1) | 115 (56.1) | 27 (56.3) | NS (0.985) |
| Previous transplantation, n (%) | 11 (4.0) | 8 (3.9) | 2 (4.2) | NS (0.933) |
| Height (cm)    | 162.0 (158.0, 168.5) | 163.0 (158.0, 170.0) | 160.6 ± 7.9 | NS (0.902) |
| Weight (kg)    | 59.62 ± 11.26 | 59.79 ± 11.37 | 58.92 ± 10.83 | NS (0.634) |
| BMI (kg/m²)    | 22.37 ± 3.36 | 22.27 ± 3.29 | 22.80 ± 3.65 | NS (0.326) |
| <18.5          | 17.19 ± 1.07 | 17.09 ± 1.11 | 17.62 ± 0.85 | NS (0.332) |
| 18.5–22.9      | 20.85 ± 1.28 | 20.81 ± 1.27 | 21.02 ± 1.32 | NS (0.462) |
| 23.0–24.9      | 23.85 ± 0.56 | 23.89 ± 0.57 | 23.61 ± 0.51 | NS (0.168) |
| ≥25.0          | 27.59 ± 2.00 | 27.39 ± 1.93 | 28.22 ± 2.21 | NS (0.237) |
| URR (%)        | 76.22 ± 8.25 | 78.22 ± 7.51 | 73.16 ± 8.61 | 0.048 |
| HGB (g/L)      | 104.0 (90.5, 113.0) | 105.0 (91.5, 113.0) | 100.5 (86.0, 113.8) | NS (0.292) |
| ALB (g/L)      | 41.0 (38.5, 43.5) | 41.2 (39.1, 44.1) | 39.9 (36.8, 41.8) | 0.004 |
| CHOL (mmol/L)  | 3.51 (3.02, 4.05) | 3.47 (3.02, 4.04) | 3.69 (3.02, 4.05) | NS (0.433) |
| TG (mmol/L)    | 1.35 (0.95, 1.80) | 1.21 ± 0.24 | 1.21 ± 0.25 | NS (0.250) |
| Ca (mmol/L)    | 1.87 ± 0.51 | 1.88 ± 0.52 | 1.84 ± 0.48 | NS (0.581) |
| PTH (pmol/L)   | 25.89 (15.07, 45.19) | 25.81 (15.45, 46.23) | 26.05 (11.08, 42.90) | NS (0.533) |
| CRP (mg/L)     | 3.22 (1.75, 6.54) | 2.97 (1.72, 5.73) | 4.57 (1.80, 9.72) | NS (0.069) |
| Comorbidities, n (%) |              |                        |                   |    |
| DM             | 54 (21.3) | 37 (18.0) | 17 (35.4) | 0.011 |
| HTN            | 98 (38.7) | 78 (38.0) | 20 (41.7) | NS (0.742) |
| CVD            | 30 (11.1) | 15 (7.3) | 13 (27.1) | <0.001 |
| HF             | 68 (26.9) | 44 (21.5) | 24 (50.0) | <0.001 |
| Vascular access, n (%) |              |                        |                   |    |
| AVF            | 184 (72.7) | 146 (71.2) | 38 (79.8) | NS (0.287) |
| TCC            | 55 (21.7) | 46 (22.4) | 9 (18.8) | NS (0.699) |
| JVC            | 10 (4.0) | 9 (9.0) | 1 (10.0) | – |
| FVC            | 2 (0.8) | 2 (100.0) | 0 | – |
| AVF graft      | 2 (0.8) | 2 (100.0) | 0 | – |
| Follow-up (months) | 28 (15.42) | 26 (15.41) | 33 (20, 47) | NS (0.135) |
| PD duration (months) | 32 (17.47) | 28 (17.46) | 36 (23, 49) | NS (0.174) |

All data were shown as n (%), mean ± SD, or median (Q1, Q3). *\( P \)-value is associated with independent sample t-tests/Mann–Whitney tests between the nonpneumonia and pneumonia groups. NS: No statistical significance; BMI: Body mass index; URR: Urea reduction ratio; Ca: Calcium; P: Phosphorus; PTH: Parathyroid Hormone; CRP: C-reaction protein; DM: Diabetes mellitus; HTN: Hypertension; CVD: Cardiovascular disease; HF: Heart failure; AVF: Arteriovenous fistula; TCC: Tunneled cuffed catheter; JVC: Jugular vein catheter; FVC: Femoral vein catheter; PD: Peritoneal dialysis; SD: Standard deviation; HGB: Hemoglobin; ALB: Albumin; TG: Triglyceride; CHOL: Cholesterol.
The 18.97% of the study participants (48 cases) were hospitalized with pneumonia. The overall cumulative probability of pneumonia-free survival was 0.871, 0.778, and 0.762 at 12, 36, and 53 months, respectively, while for the CVD group, the cumulative probabilities were 0.638 and 0.493 at the 12th and 18th months (P < 0.001 vs. non-CVD group) [Figure 1]. After adjusting for multiple covariates, patients with increased BMI (per 1 unit higher kg/m²) were associated with a higher risk of pneumonia-related hospitalization (HR 1.103, 95% CI [1.047–1.162]; P < 0.001), with this risk being higher for patients in the CVD group (HR 1.371, 95% CI [1.089–1.726]; P = 0.007). Higher levels of ALB (per g/L) were a protective factor for pneumonia-related hospitalizations overall and in non-CVD patients (HR 0.911, 95% CI [0.841–0.987]; P = 0.022 vs. HR 0.903, 95% CI [0.830–0.982]; P = 0.018). HF was also a risk factor for all of the patients (HR 2.719, 95% CI [1.580–4.679]; P < 0.001), and more than twice this risk could be observed in CVD patients (HR 5.418, 95% CI [1.609–18.244]; P = 0.006). The association between higher baseline levels of CRP with pneumonia-related hospitalizations could only be observed in CVD group. Microbiologic spectrum indicated that 56.25% of the pneumonia patients had organism-positive results, most of which were attributed to fungal infection (29.17%), followed by Gram-negative and Gram-positive bacterial infections (14.48% and 12.5%, respectively).

The overall cumulative survival proportions were 0.960 at the 12th month and 0.927 at the 36th month, while 0.872 and 0.760 (pneumonia vs nonpneumonia subgroup, P < 0.001) for pneumonia-related hospitalization group, respectively. After multivariable regression adjustments, pneumonia-related hospitalization was associated with 3.3-fold increased risk for all-cause mortality (HR 4.349, 95% CI [1.568–12.062]; P = 0.004). Meanwhile, elder age (per 1 year increase), male gender, and higher levels of CHOL (per unit higher mmol/L) were associated with higher risk of mortality among MHD patients (HR 1.074, 95% CI [1.021–1.130]; P = 0.006 vs. HR 5.173, 95% CI [1.174–22.794]; P = 0.030 vs. HR 2.586, 95% CI [1.417–4.719] P = 0.002). Conversely, ALB was still shown to be a protective element for overall survival (HR 0.873, 95% CI [0.785–0.971]; P = 0.031).

Pneumonia-related hospitalization was found to be frequent among MHD patients, of which more than one-fifth has experienced this common event in a total of 4.5 years of follow-up. Experience of a pneumonia-related hospitalization was associated with lower overall survival. Better nutritional status (higher levels of serum ALB) was protective in avoiding pulmonary infection and associated with improved survival. Microbial testing revealed high prevalence of hospital-acquired pulmonary infection in MHD patients.

This study explored clinical characteristics of pneumonia-related hospitalization among MHD patients from a Chinese hospital-based HD center. We found a similar prevalence of pneumonia-related hospitalization to that from a large-scale study on hospital-acquired infection among chronic HD patients.[3] Meanwhile, the distinctive microorganism distribution needs further exploration, as the majority were staphylococcus species and fungal infection. Increased BMI was found associated with higher risk for incidence of pneumonia-related hospitalization, which needs further verification due to an unbalanced BMI distribution in our study. Higher risk of HF from pneumonia might be attributed to alveoli flooding and the reduced ability to clear microorganisms.[4] Furthermore, DM increases the susceptibility to respiratory infections and thus is identified as an independent risk factor for pulmonary infections. Serum ALB has certain protective effects including transporting hormones, fatty acids, biliary salts, bilirubin, and ions, maintaining acid–base balance, and exerting antioxidants.[5] High infection rate of staphylococcus species might be explained by frequent exposure to healthcare-related infection through prolonged blood exposure, vascular access and many ports in the extracorporeal circuit, and close contact with health-care stuff. Moreover, the high fungal infection rate could be partially explained by ESRD patients experiencing mouth dryness and dental plaque formation, thus at risk of oral fungal infection.

Figure 1: Kaplan–Meier survival analysis showing cumulative pneumonia-free survival ([a] for all the patients; [b] by baseline cardiovascular disease category).
This study has some limitations, including that it is an observational single-center study with an unbalanced gender distribution, and there is a possibility of overdiagnosed pneumonia and a lack of dynamic change of laboratory tests. However, the long-term follow-up, relatively accurate diagnosis of pneumonia, and stable MHD patients under regular health-care education and management contribute to the reliable results.

In conclusion, pneumonia-related hospitalizations are frequent and shown to be associated with many comorbidities among MHD patients. Further, a pneumonia-related hospitalization during MHD treatment might result in poorer survival outcomes. It is our intent that the identification of risk factors among different subgroups and exploration of their microbiologic spectrum will increase the awareness of early prevention and treatment for such conditions.

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**Conflicts of interest**

There are no conflicts of interest.

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