Efficacy and safety of caspofungin for patients with hepatic insufficiency

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Abstract

Background: To observe the changes of hepatic function and efficacy of conventional dosage of caspofungin in the treatment of patients with different Child–Pugh scores.

Methods: In total, 200 patients (Child–Pugh A group: 66 patients, Child–Pugh B group: 83 patients, Child–Pugh C group: 51 patients) treated with caspofungin from May 2018 to March 2021 in the Second Affiliated Hospital of Chongqing Medical University were enrolled. Main investigation items were as follows: sex, age, weight, duration of treatment, dosage, department, underlying diseases, risk factors for fungal infection, albumin, liver enzyme, total bilirubin, serum creatinine, estimated glomerular filtration rate. To investigate the changes of liver, kidney function tests and efficacy during the treatments of caspofungin. Patients were divided into three groups according to the duration of treatment of caspofungin: 1-week group, 2-week group and 3-week group, respectively.

Results: In the three groups, albumin, liver enzyme levels, total bilirubin and serum creatinine, estimated glomerular filtration rate had no significant difference (P > 0.05). The efficacy of different Child–Pugh scores and different duration of treatment was also significantly different (P > 0.05).

Conclusions: Caspofungin is well tolerated and highly effective. And it will not exacerbate the hepatic and renal function when administered with the not-reducing dose, which indicate the clinical application value of caspofungin. Besides, extending the treatment duration has little effect on improving the efficacy of caspofungin. The drug should be withdrawn timely according to the patients’ clinical condition in order to reduce the adverse reactions and economic burden.

Keywords: Hepatic insufficiency, Child–Pugh score, Caspofungin, Dosage, Efficacy

Background

Since the start of the new millennium, invasive fungal infection (IFI) has drastically increased. IFI related mortality rates is 27.6%, there are about 100, 000 in-patients with IFI every year, and the annual cost of treating IFI in the United States is more than $7 billion [1]. Therefore, the selection of appropriate and effective antifungal drugs is an important factor to alleviate morbidity and economic burden of patients.

Currently available antifungal agents for IFIs includes echinocandins, polyenes, flucytosine, triazoles. But, a series of adverse drug reactions (ADRs) were followed with the widespread use of antifungal drugs. The most common ADRs are hepatotoxicity, nephrotoxicity and hypokalemia [2–4].

Caspofungin, as the representative of echinocandins, is generally well tolerated and safety [5, 6]. The most common abnormal laboratory index about caspofungin is elevation of liver function values, manifested by increased serum alkaline phosphatase and transaminase...
concentrations, and the increase of serum creatinine and blood urea nitrogen [7, 8].

However, the research on the application of caspofungin in patients with hepatic insufficiency (HI) is insufficient. In order to guide the clinical diagnosis and treatment of antifungal drugs in patients with HI. This study collected relevant clinical cases, revealed the clinical effect of caspofungin in patients with HI, and analyzed the changes of laboratory indexes such as liver and kidney function in patients treated with caspofungin. The report is as follows.

Materials and methods
Inclusion criteria and study design
This study was a retrospective single-center analysis, designed to estimate the changes of hepatic function and efficacy of caspofungin (Cancidas®, Merck & Co. Inc., Kajing®, Jiangsu Hengrui Medicine Co. Ltd) used for the confirmed, clinically diagnosed and suspected of IFI in the Second Affiliated Hospital of Chongqing Medical University during May 2018 to March 2021. Clinical profiles and laboratory parameters of the patients, were evaluated. All patients aged >18 years, treatment duration ≥ 7 days, matched with The Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the 6th revision), Guidelines for the diagnosis and treatment of Invasive fungal infection in critical ill patients (2007) were included in the study.

The Child–Pugh score was graded as 5–6 points for Child–Pugh A, 7–9 points for Child–Pugh B, and 10–15 points for Child–Pugh C. Patients were be divided into mild, moderate, or severe by the corresponding Child–Pugh score A, B and C.

The standard dose of caspofungin to treat IFI was a 70-mg loading dose followed by a once-daily maintenance dose of 50 mg infused over 1 h. All patients were administered with caspofungin. Efficacy was assessed in all patients at the end of caspofungin therapy and during the treatment. One hundred and fourteen (57%) with clinical diagnosis, seventy-four (37%) with suspected diagnosis and confirmed IFI were administered caspofungin as primary therapy. One hundred and fourteen (57%) with clinical diagnosis, seventy-four (37%) with suspected diagnosis patients were administered caspofungin empirically.

Dose and duration of treatment
The mean duration of caspofungin treatment was 16.8 days (range 7–62 days). Caspofungin therapy was started at a dose of 70 mg followed by 50 mg/day in 166 (83%) patients. Twenty-six (13%) patients received a 50 mg maintenance dose of caspofungin daily. Eight (4%) received caspofungin 50 mg/day, following a loading dose of 100 mg on day 1.

Changes of liver and kidney function
During the treatment, the doctor would withdraw caspofungin according to the general condition, laboratory examination parameters, imaging examinations or economic reasons of the patients. Therefore, based on the treatment duration, patients were divided into 1-week group, 2-week group and 3-week group (Table 1).

The Changes of liver and kidney function of 1-week group were shown in Table 2. ALP, GGT and Scr in Child–Pugh A patients and GGT in Child–Pugh C patients changed significantly during the treatment.

Statistical analysis
Statistical analysis was performed through IBM SPSS Statistics 21. The enumeration data were expressed as percentage (%), and the measurement data as median (quartile) (M, P25-P75), Friedman test was used to compare the changes of various parameters in different times during medication, and Wilcoxon signed-rank test was used to compare the differences between the two groups. In order to avoid Type I error caused by pairwise comparison of multiple samples, Bonferroni’s correction was needed, P values < 0.05 were regarded as statistically significant. Chi-square test was used to compare the efficacy, P values < 0.05 indicated that the difference was statistically significant.

Results
Patient characteristics
Characteristics of the 200 patients evaluated in the study were shown in Table 1. Fifty-four (27%) patients had suffered from hematologic malignancies, fifty-one (25.5%) patients had liver cirrhosis, followed by severe pulmonary diseases (18.5%) and malignancies (10%). Pulmonary invasive fungal infection is the most common, with a total of 69.5%, followed by digestive tract (24%), blood (3.5%), urinary tract (1%). Six (3%) patients with confirmed IFI were administered caspofungin as primary therapy. One hundred and fourteen (57%) with clinical diagnosis, seventy-four (37%) with suspected diagnosis patients were administered caspofungin empirically.
Table 1  General characteristics of patients

| Characteristic                        | Child–Pugh classification | Total (N = 200, %) | P  | Statistic (X²/F) |
|---------------------------------------|---------------------------|--------------------|----|-----------------|
|                                       | A (n = 66)                | B (n = 83)         | C (n = 51) |                |
| Sex                                   | Female                    | 36                 | 48  | 36              | 120 (60) | 0.186 | 3.363 |
| Age                                   | M (P25-P75)               | 58 (42–72)         | 59 (48–68) | 49 (43–61) | –        | 0.015 | 4.319 |
| Weight                                | M (P25-P75)               | 56.6 (50–66)       | 58.6 (50–65) | 58.6 (54–65) | –        | 0.376 | 0.984 |
| Period of treatment                   |                           |                    |                |                |          |       |       |
| 1 week                                |                           | 26                 | 36  | 17              | 79 (39.5) | 0.514 | 1.333 |
| 2 weeks                               |                           | 22                 | 28  | 22              | 72 (36)  | 0.469 | 1.516 |
| 3 weeks                               |                           | 18                 | 19  | 12              | 49 (24.5) | 0.812 | 0.416 |
| Department                            |                           |                    |                |                |          |       |       |
| Infectious Diseases                   |                           | 6                  | 24  | 44              | 74 (37)  | 0.000 | 77.503 |
| Hematology                            |                           | 36                 | 20  | 1               | 57 (28.5) | 0.000 | 40.389 |
| ICU                                   |                           | 2                  | 13  | 1               | 16 (8)   | 0.003 | 11.364 |
| Respiratory                           |                           | 4                  | 12  | 4               | 20 (10)  | 0.198 | 3.234 |
| Nephrology                            |                           | 3                  | 2   | 0               | 5 (2.5)  | 0.375 | 2.091 |
| Rheumatology and Immunology           |                           | 2                  | 2   | 0               | 4 (2)    | 0.683 | 1.310 |
| Others                                |                           | 13                 | 10  | 1               | 24 (12)  | 0.014 | 8.570 |
| Underlying disease                    |                           |                    |                |                |          |       |       |
| Cirrhosis of the liver                |                           | 0                  | 10  | 41              | 51 (25.5) | 0.000 | 111.386 |
| Haematological malignancy             |                           | 34                 | 19  | 1               | 54 (27)  | 0.000 | 37.058 |
| Severe pulmonary disease              |                           | 11                 | 24  | 2               | 37 (18.5) | 0.001 | 13.308 |
| Cancer                                |                           | 6                  | 14  | 0               | 20 (10)  | 0.008 | 10.077 |
| Sepsis                                |                           | 1                  | 0   | 5               | 6 (3)    | 0.003 | 8.708 |
| Acute pancreatitis                    |                           | 1                  | 3   | 1               | 5 (2.5)  | 0.853 | 0.719 |
| Solid organ transplantation            |                           | 4                  | 0   | 0               | 4 (2)    | 0.015 | 5.941 |
| Autoimmune disease                    |                           | 3                  | 2   | 0               | 5 (2.5)  | 0.375 | 2.091 |
| Chronic kidney disease                |                           | 2                  | 1   | 0               | 3 (1.5)  | 0.616 | 1.509 |
| Atherosclerotic vascular disease      |                           | 2                  | 1   | 0               | 3 (1.5)  | 0.616 | 1.509 |
| Others                                |                           | 2                  | 9   | 1               | 12 (6)   | 0.077 | 5.103 |
| Risk-factor for fungal infection      | Broad-spectrum antibiotic | 64                 | 81  | 51              | 196 (98) | 0.683 | 1.310 |
|                                       | Corticosteroid            | 39                 | 42  | 2               | 83 (41.5) | 0.000 | 40.910 |
|                                       | Immunosuppression         | 25                 | 19  | 2               | 46 (23)  | 0.000 | 18.733 |
|                                       | Central venous line       | 31                 | 42  | 33              | 106 (53) | 0.142 | 3.960 |
|                                       | Recent surgery            | 5                  | 12  | 1               | 18 (9)   | 0.041 | 6.268 |
|                                       | Tracheal intubation       | 8                  | 31  | 6               | 45 (22.5) | 0.000 | 17.943 |
|                                       | Malignancy                | 6                  | 14  | 2               | 22 (11)  | 0.055 | 5.775 |
|                                       | Diabet                   | 12                 | 12  | 4               | 28 (14)  | 0.285 | 2.579 |
|                                       | Transplant recipient      | 4                  | 0   | 0               | 4 (4)    | 0.015 | 5.941 |
|                                       | HIV                       | 0                  | 2   | 1               | 3 (1.5)  | 0.481 | 1.560 |
| Hepatoprotective drugs                | Yes                       | 35                 | 60  | 48              | 143 (71.5) | 0.000 | 18.074 |
| Diagnostic grades of IFI              | Confirmed                 | 2                  | 8   | 2               | 12 (6)   | 0.023 | 3.319 |
| Infection site                        | Clinical diagnosis        | 31                 | 47  | 36              | 114 (57) | 0.038 | 6.556 |
|                                       | Suspected diagnosis       | 33                 | 28  | 13              | 74 (37)  | 0.018 | 8.063 |
|                                       | Pulmonary                 | 54                 | 58  | 27              | 139 (69.5) | 0.003 | 12.327 |
|                                       | Digestive tract           | 10                 | 16  | 22              | 48 (24)  | 0.001 | 14.088 |
|                                       | Blood                     | 1                  | 5   | 1               | 7 (3.5)  | 0.260 | 2.693 |
|                                       | Urinary tract             | 0                  | 1   | 1               | 2 (1)    | 0.725 | 1.408 |
|                                       | Others                    | 1                  | 3   | 0               | 4 (2)    | 0.462 | 1.681 |
Table 2 Comparison of the changes of liver and kidney function in patients with different Child–Pugh scores in the 1 week group (M (P25–P75))

| Group | Time | Albumin g/L | ALT U/L | AST U/L | ALP U/L | GGT U/L | TBIL mmol/L | Scr mmol/L | eGFR ml/min |
|-------|------|-------------|---------|---------|---------|---------|------------|------------|-------------|
| A     | D0   | 33.7 (29–37) | 28.0 (13–60) | 200 (16–40) | 85.0 (72–133) | 68.0 (31–191) | 9.0 (5–13) | 62.9 (53–85) | 78.8 (52–96) |
|       | D1   | 33.3 (30–35) | 24.5 (12–71) | 205 (13–38) | 85.5 (60–124) | 67.0 (29–172) | 8.8 (5–12) | 60.9 (48–86) | 87.7 (60–107) |
|       | D7   | 31.4 (29–33) | 21.5 (12–41) | 22.5 (13–40) | 80.0 (63–108) | 52.0 (22–100) | 7.9 (6–11) | 61.0 (45–71) | 94.9 (63–120) |
| X2    |      | 5.79        | 2.80     | 3.98     | 9.41     | 14.00    | 1.17       | 6.39       | 5.43        |
|       | P    | 0.06        | 0.25     | 0.14     | 0.01     | 0.01     | 0.04       | 0.06       | 0.06        |
| B     | D0   | 30.0 (28–32) | 37.5 (16–80) | 48.5 (27–84) | 115.5 (68–147) | 83.0 (29–165) | 21.1 (10–42) | 68.7 (56–100) | 81.6 (46–106) |
|       | D1   | 29.3 (26–32) | 36.0 (12–71) | 45.5 (23–99) | 114.5 (70–154) | 88.0 (34–153) | 13.8 (8–40) | 77.0 (50–106) | 79.4 (45–104) |
|       | D7   | 29.9 (28–32) | 27.5 (14–59) | 60.1 (25–86) | 112.0 (90–209) | 92.5 (37–143) | 18.2 (8–36) | 81.8 (58–112) | 77.4 (37–98) |
| X2    | 1.69  | 1.922     | 0.75     | 0.14     | 2.02     | 3.32     | 0.39       | 0.2         |
|       | P    | 0.43        | 0.382     | 0.69     | 0.93     | 0.37     | 0.21       | 0.62       | 0.61        |
| C     | D0   | 30.6 (25–34) | 21.0 (16–32) | 48.0 (28–85) | 88.0 (71–171) | 37.0 (25–85) | 163.0 (51–324) | 89.0 (54–146) | 69.6 (30–91) |
|       | D1   | 30.0 (27–35) | 22.0 (14–32) | 44.0 (30–65) | 77.0 (67–157) | 37.0 (24–60) | 156.0 (67–276) | 83.4 (62–168) | 69.7 (32–97) |
|       | D7   | 31.0 (27–34) | 17.0 (10–41) | 55.0 (33–117) | 86.0 (68–153) | 46.0 (23–66) | 162.0 (62–308) | 79.9 (64–142) | 65.0 (36–86) |
| X2    | 0.22  | 0.456     | 2.63     | 5.52     | 7.18     | 0.05     | 0.78       | 1.00        |
|       | P    | 0.89        | 0.796     | 0.27     | 0.06     | 0.03     | 0.72       | 0.68       | 0.61        |

*Bonferroni’s correction, compared with D0, the difference was statistically significant

But when making a pairwise comparison of different time points, we found that only GGT in Child–Pugh C patients changed significantly with the time. But when making a pairwise comparison of different time points, we found that the albumin levels in Child–Pugh B patients on D0 and D1 significantly less than D7 (P < 0.05). The results showed that the liver and kidney function in Child–Pugh A, B and C patients did not change significantly with time (P > 0.05).

In the 2-week group (Table 3), the albumin, ALT, AST and Scr, eGFR in Child–Pugh B patients and ALT in Child–Pugh C patients changed significantly with the time. But when making a pairwise comparison of different time points, we found that the albumin levels in Child–Pugh B patients on D1 were significantly less than D14 (P < 0.05), Scr in Child–Pugh B patients on D0 and D1 significantly larger than D7 and D14, eGFR in Child–Pugh B patients on D0 and D1 significantly less than D7 and D14, respectively (P < 0.05). The results showed that the liver and kidney function in Child–Pugh A, B

Table 3 Comparison of the changes of liver and kidney function in patients with different Child–Pugh scores in the 2-week group (M (P25–P75))

| Group | Time | Albumin g/L | ALT U/L | AST U/L | ALP U/L | GGT U/L | TBIL mmol/L | Scr mmol/L | eGFR ml/min |
|-------|------|-------------|---------|---------|---------|---------|------------|------------|-------------|
| A     | D0   | 31.8 (29–35) | 17.5 (8–35) | 19.5 (16–28) | 89.0 (59–113) | 38.0 (19–92) | 8.6 (6–15) | 56.4 (47–131) | 86.8 (38–130) |
|       | D1   | 32.4 (29–34) | 16.0 (9–31) | 16.5 (13–26) | 86.0 (74–118) | 42.0 (27–84) | 8.8 (5–14) | 57.4 (45–108) | 88.6 (38–139) |
|       | D7   | 30.1 (26–33) | 25.5 (14–48) | 20.0 (15–26) | 94.7 (81–103) | 38.5 (26–61) | 10.7 (6–15) | 69.0 (44–115) | 88.4 (41–131) |
| X2    | 6.39  | 3.38        | 4.91     | 1.41     | 2.08     | 2.35     | 0.60       | 0.96        |
|       | X2   | 3.38        | 3.11     | 3.64     | 7.61     | 10.76    | 2.35       | 3.96        |
|       | P    | 0.09        | 0.29     | 0.18     | 0.70     | 0.56     | 0.50       | 0.89       |
|       | P    | 0.09        | 0.29     | 0.18     | 0.70     | 0.56     | 0.50       | 0.89       |

*Bonferroni’s correction, compared with D0, the difference was statistically significant

* Bonferroni’s correction, compared with D1, the difference was statistically significant

* Bonferroni’s correction, compared with D0, the difference was statistically significant

* Bonferroni’s correction, compared with D1, the difference was statistically significant

* Bonferroni’s correction, compared with D0, the difference was statistically significant

* Bonferroni’s correction, compared with D1, the difference was statistically significant
and C patients had not changed significantly with time (P > 0.05).

In the 3-week group (Table 4), the albumin and Scr, eGFR levels in Child–Pugh B patients changed significantly with time. But when making a pairwise comparison of different time points, we found that albumin levels in Child–Pugh B patients on D1 were significantly less than D14 and D21 (P < 0.05), Scr levels in Child–Pugh B patients on D0 were significantly larger than D1 (P < 0.05), eGFR levels in Child–Pugh B patients on D0 and D1 significantly less than D14 and D21. The results showed that the liver and kidney function in Child–Pugh A, B and C patients had not changed significantly with time (P > 0.05).

The outcomes of treatment
At the end of treatment, efficacy with different Child–Pugh scores and different courses of treatment was 63%. There was no difference in the effective rate of patients classified as Child–Pugh A, B and C (P > 0.05). There was no difference in the effective rate of patients with 1 week, 2 weeks and 3 weeks of treatment (P > 0.05) (Tables 5, 6).

Discussion
The recent literature suggests that common adverse effects of caspofungin include elevated transaminases (ALT, AST), ALP, TBIL, Scr, fever, GI symptoms (nausea, vomiting, abdominal pain, diarrhea), phlebitis, and allergy. In HI patients, the dose should be adjusted according to Child–Pugh score. In recent years, Gustot et al. [10] found that the dose of caspofungin should not be reduced regardless of the severity of hepatic failure. In the present study, 13% patients were not given loading doses for economic reasons, pre-existing use of other antifungal drugs, or irrational dosing, but all patients (including Child–Pugh C patients) were maintained at 50 mg/day regardless of hepatic function, and no exacerbation of hepatic or renal impairment occurred regardless

Table 4 Comparison of the changes of liver and kidney function in patients with different Child–Pugh scores in the 3-week group (M (P25–P75))

| Group | Time | Albumin g/L | ALT U/L | AST U/L | ALP U/L | GGT U/L | TBIL mmol/L | Scr mmol/L | eGFR mL/min |
|-------|------|-------------|--------|--------|---------|---------|-------------|------------|-------------|
| A     | D0   | 31.7 (28–35)| 19.0 (8–28)| 18.0 (11–25)| 72.0 (65–109)| 45.0 (23–119)| 7.8 (5–18)| 78.2 (65–105)| 85.5 (31–152)|
|       | D1   | 29.5 (27–32)| 15.0 (10–43)| 19.0 (11–28)| 81.0 (58–122)| 51.0 (18–129)| 7.2 (5–17)| 65.7 (54–100)| 93.4 (41–142)|
|       | D7   | 30.1 (28–32)| 16.0 (9–26)| 21.0 (13–28)| 84.0 (59–114)| 36.0 (19–101)| 7.6 (5–15)| 67.1 (57–108)| 83.5 (27–125)|
|       | D14  | 30.2 (29–32)| 20.0 (9–31)| 20.0 (12–28)| 82.0 (61–124)| 39.0 (26–81)| 8.3 (6–13)| 62.5 (51–90)| 94.0 (37–145)|
|       | D21  | 29.5 (29–35)| 21.0 (9–38)| 27.0 (13–34)| 76.0 (67–123)| 39.0 (25–56)| 8.2 (6–12)| 54.7 (45–86)| 95.6 (36–146)|
| X²    | 4.57 | 0.65        | 1.48    | 4.15    | 1.71    | 1.21    | 7.51        | 8.08       |
| P     | 0.33 | 0.06        | 0.83    | 0.48    | 0.79    | 0.87    | 0.11        | 0.08       |
| B     | D0   | 28.0 (26–32)| 15.0 (11–55)| 24.0 (14–50)| 97.0 (63–140)| 67.0 (32–181)| 7.7 (6–11)| 67.9 (51–118)| 70.5 (38–110)|
|       | D1   | 27.1 (26–28)| 22.0 (8–57)| 24.0 (13–76)| 106.0 (67–137)| 63.1 (26–166)| 9.0 (4–12)| 62.2 (48–118)| 81.4 (42–125)|
|       | D7   | 30.1 (29–32)| 17.0 (11–48)| 22.0 (12–48)| 118.0 (71–176)| 48.0 (20–178)| 9.3 (6–11)| 58.9 (45–94)| 90.9 (56–133)|
|       | D14  | 31.6 (29–34)| 25.0 (9–56)| 23.0 (10–52)| 103.0 (72–201)| 87.0 (19–133)| 10.6 (8–16)| 52.7 (23–71)| 99.6 (43–132)|
|       | D21  | 31.1 (29–33)| 23.5 (13–47)| 22.0 (16–32)| 86.0 (70–208)| 72.0 (23–169)| 9.0 (6–14)| 53.5 (41–76)| 106.1 (37–135)|
| X²    | 17.26 | 1.65        | 3.07    | 4.61    | 2.19    | 4.60    | 12.54       | 11.1       |
| P     | 0.002 | 0.79        | 0.45    | 0.33    | 0.70    | 0.33    | 0.01        | 0.02       |
| C     | D0   | 29.4 (28–31)| 44.0 (16–71)| 56.0 (44–159)| 145.0 (99–163)| 54.0 (30–82)| 31.0 (12–400)| 60.5 (47–366)| 77.8 (14–128)|
|       | D1   | 29.6 (29–31)| 26.0 (10–52)| 56.0 (33–106)| 130.0 (116–155)| 51.0 (30–68)| 276.5 (121–417)| 60.5 (54–199)| 69.8 (3–128)|
|       | D7   | 30.5 (30–32)| 18.0 (11–41)| 55.0 (41–92)| 122.0 (91–157)| 41.0 (24–87)| 284.5 (110–393)| 68.1 (43–114)| 96.8 (53–147)|
|       | D14  | 31.0 (30–32)| 22.0 (11–41)| 47.0 (33–63)| 121.0 (112–160)| 47.0 (31–68)| 184.0 (119–358)| 53.5 (45–87)| 87.4 (47–130)|
|       | D21  | 33.0 (32–35)| 20.0 (15–40)| 55.0 (34–84)| 123.0 (92–189)| 42.0 (25–70)| 171.4 (121–407)| 60.1 (42–75)| 93.8 (61–116)|
| X²    | 9.08 | 1.93        | 2.94    | 3.34    | 1.72    | 5.49    | 3.36        | 3.58       |
| P     | 0.06 | 0.75        | 0.57    | 0.50    | 0.79    | 0.24    | 0.49        | 0.46       |

¹ Bonferroni’s correction, compared with D0, the difference was statistically significant
² Bonferroni’s correction, compared with D1, the difference was statistically significant

Table 5 Comparison of the efficacy in different Child–Pugh scores patients

| Group | Complete response | Partial response | Stable response | Progression of disease | Death | Efficient (%) |
|-------|-------------------|------------------|----------------|------------------------|-------|---------------|
| A     | 2                 | 46               | 8              | 7                      | 3     | 72.7          |
| B     | 3                 | 48               | 9              | 9                      | 14    | 61.4          |
| C     | 5                 | 22               | 11             | 6                      | 7     | 52.9          |
| X2    | 2.93              | 3.33             | 3.307          | 0.043                  | 5.479 | 7.438         |
| P     | 0.245             | 0.016            | 0.212          | 1.000                  | 0.067 | 0.114         |
| Total | 10                | 116              | 28             | 22                     | 24    | 63.0          |
of the duration. One hand, it may be related to the aggressive treatments in primary diseases, which avoided mild hepatic impairment in some patients. On the other hand, some patients were treated with hepatoprotective drugs during hospitalization for avoiding the underlying hepatic impairment [8]. Besides, in this study there were differences in the basic liver conditions between the groups, for example, 80% of patients with liver cirrhosis in grade C group, but with the use of hepatoprotective drugs, the findings suggest that the use of standard doses of caspofungin is still safe and no adjustment of dose, while the percentage of cirrhosis in the grade B group was only 12 and the use of liver-protective drugs in this subgroup was 72%, suggesting that standard-dose caspofungin remains tolerable and safe through the use of liver-protective drugs in patients with non-cirrhosis leading to abnormal liver function and graded at grade B. Therefore, our study indicates that caspofungin is safe and reliable for using in IFI patients, with minimal effect on liver function. If patients with basic HI, we should pay attention to monitoring their liver function and adding hepatoprotective drugs in time while not discontinuation of the drug.

At present, many scholars at home and abroad have conducted studies on high loading doses or high maintenance doses of caspofungin in order to further explore the maximum tolerated dose and efficacy of caspofungin. Wang Huajie et al. [11] concluded that the high dose (a loading dose of 100 mg on day 1 and maintenance dose of 70 mg/day) caspofungin group had significantly higher clearance rate of different types of fungi compared with the standard dose group, and there were no significant changes in liver and kidney function before and after treatment in both groups. In this study, due to physician decisions and the patient’s illness, 8 (4%) patients (all from the infection department, 7 with underlying liver failure and 1 with severe pulmonary infection) were administered with a loading dose of 100 mg on day 1 and a maintenance dose of 50 mg/day for 7–24 days, and 2 of these patients eventually died without further deterioration in liver function during treatment, which is consistent with the study carried by Wang, Huajie et al. It indicates that increasing the first dose of caspofungin does not aggravate patients’ hepatic impairment. However, because the sample size is small, the outcomes for these patients should be interpreted with caution. But tit can still provide a reference for future studies.

In terms of efficacy, the overall effective rate (63%) when treating with caspofungin in patients with different Child–Pugh classifications was almost consistent with the effective rate (65%) reported by Xiaohui Zhang et al. [12]. There was no difference in the efficacy of caspofungin in patients with different hepatic function grades, suggesting that even without dose reduction, grade B and C patients tolerated caspofungin not differently from grade A patients and had better treatment outcomes. The current consensus on the time frame of antifungal therapy [13] revealed that antifungal drugs should be maintained at least 2 weeks after the patient’s signs and symptoms have alleviated, laboratory parameters have improved, and microbial detection has turned negative. However, this study showed that there was no difference in the efficiency of caspofungin in the 1-week, 2-week, and 3-week antifungal treatment, indicating that patients’ symptoms and signs, laboratory indices, imaging, and pathogenesis should be followed up timely and antifungal treatment should be withdrawn according to their clinical conditions timely. Because blindly prolonging the duration of caspofungin treatment if the patients’ above monitoring indices have improved significantly does not seem to improve the patients’ outcomes significantly but increase their financial burden.

### Conclusions

Based on these limited data, it is suggested that caspofungin is well tolerated and liver function classified as Child–Pugh C should not be considered as a contraindication for caspofungin using or a criterion for dose reduction, and caspofungin should be administered in adequate doses even in HI patients to achieve better therapeutic outcomes.

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### Table 6 Comparison of the efficacy in different treatment duration

| Group       | Complete response | Partial response | Stable response | Progression of disease | Death | Efficient (%) |
|-------------|-------------------|------------------|----------------|------------------------|-------|---------------|
| 1 week      | 4                 | 46               | 12             | 9                      | 8     | 63.3          |
| 2 weeks     | 5                 | 40               | 10             | 8                      | 9     | 62.5          |
| 3 weeks     | 1                 | 30               | 5              | 6                      | 8     | 63.3          |
| X2          | 1.269             | 6.998            | 1.985          | 0.700                  | 0.690 | 1.416         |
| P           | 0.652             | 0.030            | 0.369          | 0.715                  | 0.711 | 0.084         |
| Total       | 10                | 116              | 27             | 22                     | 25    | 63.0          |
Author contributions
XR, PW and BT collected and analyzed the data; AZ and XR conceived and designed the experiments; XR and BT contributed to the writing of the manuscript; PW and AZ revised the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Committee of the Second Affiliated Hospital of Chongqing Medical University (23th, June, 2020). Informed consent to participate in the study has been obtained from participants.

Consent for publication
Not applicable.

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

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