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ORIGINAL RESEARCH

Meropenem Pharmacokinetics and Target Attainment in Critically Ill Patients

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Purpose: This study aimed to investigate the pharmacokinetics and target attainment of meropenem and compare the effect of meropenem dosing regimens in critically ill patients.

Patients and Methods: Thirty-seven critically ill patients who were administered meropenem in intensive care units were analyzed. Patients were classified according to their renal function. Pharmacokinetic parameters were assessed based on Bayesian estimation. The target attainment of 40%fT > MIC (fraction time that the free concentration exceeds the minimum inhibitory concentration) and 100%fT > MIC with the pathogen MIC of 2 mg/L and 8 mg/L were specially focused. Furthermore, the effects of standard dosing (1g meropenem, 30 min intravenous infusion every 8h) and non-standard dosing (dosage regimens except standard dosing) were compared.

Results: The results showed that the values of meropenem clearance (CL), central volume of distribution (V1), intercompartmental clearance (Q), and peripheral volume of distribution (V2) were 3.3 L/h, 9.2 L, 20.1 L/h and 12.8 L, respectively. The CL of the patients among renal function groups was significantly different ($p < 0.001$). The tow targets attainment for the pathogen MIC of 2 mg/L and 8 mg/L were 89%, 73%, 49% and 27%, respectively. The severe renal impairment group has higher fraction of target attainment than the other group. The standard dosing achieved the target of 40%fT > 2/8 mg/L (85.7% and 81%, respectively) and patients with severe renal impairment achieved the target fraction of 100% for 40%fT > MIC. Additionally, there was no significant difference between standard and non-standard dosing group in target attainment.

Conclusion: Our findings indicate that renal function is an important covariate for both meropenem pharmacokinetics parameters and target attainment. The target attainment between standard and non-standard dosing group was not comparable. Therefore, therapeutic drug monitoring is indispensable in the dosing adjustment for critically ill patients if it is available.

Keywords: meropenem, critically ill patients, pharmacokinetics, therapeutic drug monitoring

Introduction

Meropenem, a broad-spectrum carbapenem antibiotic, is commonly used in intensive care units (ICUs) for the treatment of gram-negative bacillus and gram-positive cocci infections, or as empirical treatment of severe infections.[1] It has been observed that optimal therapeutic effect of meropenem is time-dependent, with the unbound concentration of the drug needing to remain above the minimum inhibitory concentration (MIC) of the pathogens for an effective treatment. The percentage of time that the free concentration remains above the MIC (%fT > MIC) has been shown to be one of the best evaluation indexes of antibacterial effect of meropenem. Studies have defined pharmacokinetic and pharmacodynamic (PK/PD) target of meropenem as a fraction time of fT > MIC (%fT > MIC) of at least reaching over 40%, and even up to 100% for critically ill patients.[2,3]

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In order to ensure the efficacy of treatment, therapeutic drug monitoring (TDM) is often performed to guide dose adjustment for meropenem, because of altering pharmacokinetic in critically ill patients.[4] Pathophysiological changes especially alteration in renal function as well as supportive treatments may contribute to pharmacokinetic parameters therefore resulting in drug concentration over- and/or underexposure.[5,6] Studies revealed that critically ill patients were hard to reach sufficient blood concentration and had large variability between patients under standard dosing treatment.[7–9] Lisa Ehmann et al[10] found that mild renal impairment up to augmented renal function can be a risk factor for failing to reach the desired target in critically ill patients. As renal excretion is a major factor for meropenem clearance, creatinine clearance is often employed to aid in optimizing meropenem effectiveness.[11]

Determining meropenem regimens can be a difficult task, as it requires taking into account many factors such as MICs of microorganisms and renal function. For critically ill patients, the efficacy of treatment can be improved by administering 2g load dose, intravenously over 3–4 hours, or a continuous infusion of 3–4g over 24 hours.[12,13] Furthermore, a 3 hours extended infusion of 1g meropenem was found to be more beneficial than a 30 min infusion in terms of target attainment.[14] It was observed that those critically ill patients with eGFR (estimated glomerular filtration rate) > 90 mL/min/1.73 m^2 who received a short-term infusion (<60 min) were unable to achieve a probability target attainment > 90% for MIC ≥ 2 mg/L.[15] In clinical practice, dose selection of meropenem may be challenging. The data of standard dose was mainly derived from the healthy volunteers, which may reduce the success rate of treatment for critically ill patients.[2] Onichimowski et al suggested that standard dosing was beneficial for most critically ill patients with continuous renal replacement therapy (CRRT) to reach the target of 40%fT > 2 mg/L.[16] As for the ventilator-associated pneumonia patients, standard dose in 30 min infusions achieved the target fT > MIC (1mg/L) in a fraction of 74.7%. However, regarding with higher MIC (16 mg/L), an extended infusion of 2g meropenem every 8 hours reached 40%fT > MIC.[17] Therefore, further pharmacokinetic studies with different dosages, intervals, and infusion times are necessary for critically ill patients.

The aim of this study is to analyze the TDM data of ICU patients who received meropenem, calculate the pharmacokinetic parameters of meropenem through TDMx, and compare the pharmacokinetic parameters of patients with different renal function to the target attainment. We also examined the target attainment of patients with different renal function who were administered the standard dosing treatment and compared the effects of standard dosing group and non-standard dosing group.

Materials and Methods

Patients and Data Collection

We collected the critically ill patients who received meropenem treatment at ICU department of Meizhou People's Hospital between June 2021 and October 2022. Patients aged 18 years or older who received meropenem treatment for at least two days and had their serum concentration measured at least one time were included in this study. Pregnant patients or those who could not provide complete clinical data were excluded. The demographic data, laboratory examination results, medication, and clinical information were obtained from the Hospital Information System (HIS) and Laboratory Information System (LIS) of Meizhou People's Hospital. The study was conducted according to the Declaration of Helsinki and has been approved by the ethics committee of Meizhou People's Hospital (2022-C-100). Informed consent was waived due to the nature of the retrospective study.

Determination of Meropenem Plasma Concentration

The plasma level of meropenem was measured by liquid chromatography-tandem mass spectrometry (Triple Quad 4500M, SCIEX Corp, USA). Electric spray ion (ESI) was used for positive ion scanning by multiple reaction monitoring (MRM) mode, with meropenem-d6 as internal standard. The MRM transitions (m/z) of meropenem and meropenem-d6 were 384.1→141.1 and 390.2→147.2, respectively. The mobile phase contained water (0.1% formic acid) and methanol (0.1% formic acid). The flow rate was 0.5 mL/minute using a gradient elution mode. Chromatographic separation was performed in KLP-SPZ-004 column. Before measurement, the blood samples required pretreated. 25 μL of serum sample was added into a 1.5 mL centrifuge tube and then added 75 μL of internal standard solution dissolved in methanol. The

mixture was mixed on a vortex at 2500 rpm for 5 minutes, followed by centrifugation at 13,000 rpm for 5 minutes. 20 μL of supernatant and 180 μL of ultrapure water were mixed well for injection detection. The linear calibration range was 0.5–40 mg/L (r^2>0.999) with an imprecision < 5%. The recovery rate ranged from 97% to 99%. The relative standard deviation (RSD) of meropenem under different storage conditions was ≤ 7.8%.

Assessment of Renal Function

Creatinine clearance was calculated following the Cockcroft and Gault equation ($CLCR_{GG}$).[18] The patient's renal function was stratified by $CLCR_{GG}$: severe renal impairment 0–29 mL/min, moderate renal impairment > 30–59 mL/min, mild renal impairment > 60–89 mL/min, normal renal function > 90–129 mL/min, and augmented renal function > 130 mL/min.[19]

Pharmacokinetic/Pharmacodynamic Target Attainment

The effect of meropenem depends on the time that the free drug concentration exceeds the minimum inhibitory concentration (MIC) (fT > MIC).[2] According to the MIC data on EUCAST database (http://www.eucast.org), MIC values of ≤ 2 mg/L or MIC ≤ 8 mg/L are considered suitable susceptibility breakpoints for most bacterium including P. *aeruginosa* strains. A relative conservative target of 40%fT > MIC and a higher target of 100%fT > MIC were selected as the PK/PD target in this study.

Pharmacokinetic/Pharmacodynamic Parameter Calculation

A friendly open web-based tool, TDMx (http://www.tdmx.eu/), was used to evaluate pharmacokinetic parameter of meropenem based on Bayesian model.[20] The results estimated by TDMx and the algorithms were up to academic and industry standard for parametric population PK modelling. After inputting the patient's covariates, the model predicted the PK parameters and the fraction of fT > MIC under different MICs. The %fT > MICs (0.25, 0.5, 1, 2, 4, 8, 16, 32 mg/L) were calculated.

Statistical Analysis

Continuous normally distributed variables and non-normally distributed variables were presented as means ± standard deviations (SD) and median [interquartile ranges], respectively. Categorical variables were presented as counts and frequencies (%). Kruskal–Wallis test was applied to compare the pharmacokinetic parameters between various renal function groups. Continuous variables were examined using Student's *t*-test or Mann–Whitney *U*-test depending on the data distribution. Categorical data were tested by Chi-square. $P < 0.05$ was considered statistically significant for all tests. All statistical analysis were performed with the IBM SPSS statistics 22.0 (IBM Corp, New York, USA).

Results

Patient Characteristics and Clinical Data

37 critically ill patients (29 males) with a total of 71 TDM samples were included in this analysis. The median age was 69.0 (64.5–78.0) years and a majority of patients had different degrees of renal impairment (86.5%). The types of infection were pulmonary infection (n=32) and sepsis (n=5). The mean duration of meropenem treatment was 8.3 ± 3.9 days. The patients' demographic and clinical characteristics are shown in Table 1.

Comparison of Pharmacokinetic Parameter Estimates for Meropenem Based on Renal Function

Pharmacokinetic parameters estimate for meropenem are presented in Table 2. The median clearance of meropenem was 3.3 (2.5–12.4) L/h. Compared to the normal renal function group and the mild renal impairment group, the severe renal impairment group had lower meropenem clearance (2.6 [1.8–3.7] vs 14.9 [7.24–21.4], $p = 0.028$; 2.6 [1.8–3.7] vs 14.1 [9.44–26.1], $p = 0.007$). However, there was no significant difference in central volume of distribution (V1), inter-compartmental clearance (Q), and peripheral volume of distribution (V2) among all renal function groups.

Table 1 Characteristics of Patients

Variables	Value
Number of patients (n)	37
Age (years)	69.0(64.5–78.0)
Male gender	29(78.4%)
Height (cm)	165.0(160.0–170.0)
Weight (kg)	57.1±10.0
BMI (kg/m^2)	21.3±3.0
Serum creatinine (μmol/L)	191.2(73.0–268.5)
Creatinine clearance (mL/min)	25.8(14.0–68.1)
Renal function	
Normal renal function	5(13.5%)
Mild renal impairment	5(13.5%)
Moderate renal impairment	7(18.9%)
Severe renal impairment	20(54.1%)
Supportive therapy	
Renal replacement therapy	5(13.5%)
Mechanical Ventilation	34(91.9%)
Duration of meropenem treatment (days)	8.3±3.9
Initial daily maintenance dose of meropenem (g)	
0.5g	1(2.7%)
2g	5(13.5%)
3g	31(83.8%)
Type of infection	
Pulmonary infection	32(86.5%)
Sepsis	5(13.5%)
Infection species	
Gram negative bacillus	15(40.5%)
Gram positive cocci	2(5.4%)
Unknown	20(54.1%)

Notes: Data are presented as mean ± standard deviation, median [interquartile range] or n (%).
Abbreviation: BMI, body mass index.

Table 2 Pharmacokinetic Parameters Estimate for Meropenem

	All	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment	*p*
CL (L/h)	3.3(2.5–12.4)	14.9(7.24–21.4)	14.1(9.44–26.1)	7.15(2.69–12.4)	2.6(1.8–3.7)[ab]	<0.001
V1(L)	9.2±2.6	10.9±2.5	7.3±2.1	7.8±2.7	9.8±2.4	0.069
Q (L/h)	20.1±4.9	20.5(15.35–27.1)	18.6(15.6–19.3)	19.5(16.0–24.3)	20.35(18.7–23.6)	0.492
V2(L)	12.8(11.2–14.7)	13.2(10.65–14.5)	12.7(10.51–15.9)	12.3(11.1–14.6)	13.2(12.5–16.2)	0.674

Notes: Kruskal–Wallis ` for groups comparisons: [a]$p = 0.028$ for severe renal impairment group vs normal renal function group, [b]$p = 0.007$ for severe renal impairment group vs mild renal impairment. Data are presented as mean ± standard deviation, median [interquartile range].
Abbreviations: CL, Drug Clearance; V1, Central Volume of Distribution; Q, Intercompartmental Clearance, V2, Peripheral Volume of Distribution.

Pharmacokinetic/Pharmacodynamic Target Attainment

The results of achieving 40%fT > MIC and 100%fT > MIC for various meropenem MICs are presented in Figure 1 and the Supplementary Tables 1 and 2. The tow targets (40% and 100%fT > MIC) attainment for the pathogen MIC of 2 mg/L and 8 mg/L were 89%, 73%, 49% and 27%, respectively. For MIC < 4 mg/L, the fraction of achieving 40%fT > MIC is greater than 60%. The severe renal impairment group has higher fraction for 40%fT > MIC than other group among

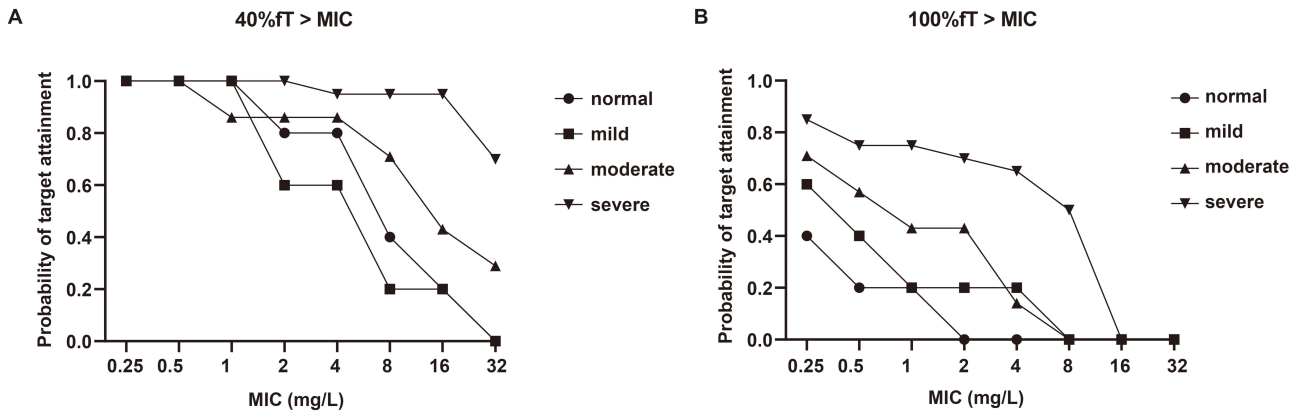

Figure 1 Probability of target attainment of different renal function groups for targets of 40%fT > MIC (**A**) and 100%fT > MIC (**B**).
Abbreviations: normal, normal renal function group; mild, mild renal impairment group; moderate, moderate renal impairment group; severe, severe renal impairment group.

different meropenem MICs. The results for 100%fT > MIC in severe renal impairment group are similar to those of 40% fT > MIC.

In addition, the fraction of the two target under standard dosing between each renal function groups was summarized, with special focus on 2 mg/L and 8 mg/L. The standard dosing regimen reached 85.7% and 81% for target of 40%fT > MIC, respectively. For the target of 100%fT > MIC, it achieved the fraction of 47.6% and 23.8%, respectively. Detailed information of the target attainment between each group is described in Table 3.

Comparison of the Effects Between Dosage Regimens of Meropenem

According to the recorded dosage regimens data, the patients were divided into standard dosing group (n=21) and non-standard dosing group (n=16). The pharmacokinetic parameters, blood laboratory tests before/after meropenem administration, target attainment and duration of medication were assessed between the two groups, and the results were described in Table 4. There were statistically significant differences in CL, white cell counts after meropenem treatment and duration of medication between the two groups, and no significant differences were observed in the other variables.

Discussion

Our study indicated that renal function had significant effect on meropenem clearance and target attainment in critically ill patients. Standard dosing can achieve the target of 40%fT > MIC. There was no significant difference between standard and non-standard dosing group in target attainment.

Meropenem is widely used in the intensive care units against infection. Pharmacokinetic evaluation of meropenem is helpful for dose adjustment in critically ill patients. The pharmacokinetics of meropenem in critically ill patients are highly heterogeneous, and the pharmacokinetic parameters derived from healthy volunteers are not suitable for guiding the use of meropenem in critically ill patients.[21] In addition to pathophysiological changes, supporting therapies such as

Table 3 Target Attainment Under the Regimen of Standard Dosing

Renal Function	40% fT > MIC		100% fT > MIC	
	2 mg/L	8 mg/L	2 mg/L	8 mg/L
All (n=21)	85.7	81	47.6	23.8
Normal renal function (n=3)	66.7	33.3	0	0
Mild renal impairment (n=5)	60	20	20	0
Moderate renal impairment (n=4)	100	75	50	0
Severe renal impairment (n=9)	100	100	77.8	55.6

Table 4 The Effects of Standard Dosing and Non-Standard Dosing Group

Variables	Standard Dosing Group (n=21)	Non-Standard Dosing Group (n=16)	*P*
CL	6.48(2.92–13.25)	2.66(1.58–3.61)	**0.013**
V1	9.03±2.38	9.42±3.0	0.657
Q	19.73±2.91	20.51±6.72	0.664
V2	12.7(11.55–13.8)	12.85(10.75–16.53)	0.736
White cell counts-before meropenem treatment	12.1(11.55–13.8)	13.1(10.48–19.6)	0.244
White cell counts-after meropenem treatment	7.4(5.7–15.25)	13.1(10.05–17.6)	**0.037**
PCT-before meropenem treatment	4.34(0.58–24.01)	5.03(2.53–26.46)	0.69
PCT-after meropenem treatment	0.84(0.21–2.73)	1.61(0.76–3.42)	0.257
CRP-before meropenem treatment	178.3±119.49	126.05±86.32	0.148
CRP-after meropenem treatment	75.45(22.78–159.51)	81.39(62.49–139.35)	0.854
40%fT > MIC (2 mg/L)	18(85.7%)	15(93.8%)	0.618
40%fT > MIC (8 mg/L)	14(66.7%)	13(81.3%)	0.461
100%fT > MIC (2 mg/L)	10(47.6%)	8(50%)	0.886
100%fT > MIC (8 mg/L)	5(23.8%)	5(31.3%)	0.716
Duration of meropenem treatment (days)	7.2±3.6	9.8±3.8	**0.046**

Note: *P* value < 0.05 is highlighted in bold.
Abbreviations: PCT, procalcitonin; CRP, C-reaction protein.

extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) also complicate the pharmacokinetics of meropenem.[22,23] The current study found that renal function had greatest impact on meropenem clearance (CL) among other pharmacokinetic parameters, which was similar to another study.[24] CL of normal renal function to moderate renal impairment was in the reported range 4.7–15.4 L/h,[25] while the median CL of the severe renal function group was lower than 3 L/h. The lower value of CL in the severe renal function group partly associated with worse renal function or older age compared to the reported population.[9,26] Previous studies had identified creatinine clearance as a determinant factor for meropenem treatment, which influenced the PK/PD target attainment.[24,27] There was no significant difference in V1, Q, and V2 in renal function groups. Generally, the volume of distribution of meropenem in healthy people were about 15–20 L,[28] while in critically ill patients it may increase to 21.7–34.4 L.[29,30] Conversely, the mean volume of distribution in our study was decreased at 9.2 ± 2.6 L, which was approximately close to the results obtained in Singaporean critically ill patients.[31] And Ehmann et al reported that the critically ill patients without CRRT had a lower volume of distribution (7.89 L) and body weight and albumin were factors influencing V1 and V2, respectively.[24] Therefore, the difference of pharmacokinetic parameters of meropenem may be mainly due to the different state of the study population and treatment schemes.

In regards to analysis PK/PD target, we considered investigating the percentage of 40%fT >MIC and 100%fT >MIC. Overall, our analysis revealed that meropenem can reach the target of 40%fT >MIC when the MIC range was from 0.25 mg/L to 32 mg/L. Conversely, it's unable for meropenem to achieve considerable fraction of 100%fT >MIC within the same MIC range. Similarly to our work, Lisa Ehmann et al found the fraction of 100%fT >MIC was 48.4% and 20.6% for MICs of 2 mg/L and 8 mg/L, respectively.[10] Also, the target attainment of 100%fT >MIC studied by Carlier et al was 55%.[32] To our knowledge, various complicated factors affect the realization of PK/PD target in critically ill patients, including states or severity of the illness, infection species, renal function, with/without supportive treatment, and fluid retention, etc.[32–35] Notably, renal function determined by $CLCR_{GG}$ had been identified to influence the meropenem plasma exposure.[11,27] The patients included in this study covered the renal function from normal to severe renal impairment. We further analyzed the probability of target attainment of the two targets in different renal function groups (see the Supplementary Tables 1 and 2). Lisa Ehmann et al revealed that attainment of 100%fT >MIC (8 mg/L) in normal to moderate renal function group was 3.5%, 4.6% and 51%, respectively.[10] However, compared to our results, it only reached 50% in severe renal impairment group and 0% in other groups. There is still much debate regarding dosing adjustment and methods of drug delivery for critically ill patients. Some studies have suggested that continuous infusion

was superior to intermittent or standard dosing to improve clinical outcomes,[8,36] while Dulhunty J M's publication showed that there was no difference between continuous infusion and intermittent dosing.[37] The majority of the included patients in our study were treated with standard dosing and those patients were only able to achieve the target of 40%fT >MIC with the pathogens of 2 mg/L and 8 mg/L. In order to achieve the target of 100%fT >MIC for susceptible pathogens, 2 to 3 fold standard dose was required in critically ill patients.[38] Regarding renal function, the severe renal impairment group had the highest fraction of 40%fT >MIC compared to other groups.

Standard dosing of meropenem is commonly implemented in ICU patients[39] though studies had indicated that standard dosing could not result in sufficient meropenem exposure.[40] The comparison of the efficacy of patients treated with standard dosing or non-standard dosing revealed that the median CL of the non-standard dosing group is lower than the standard group, potentially due to variations in the regimens. Laboratory infection index show no difference in the white cell counts before meropenem treatment between the two groups, while the median of the white cell counts after meropenem treatment in the standard dosing group was lower and in the normal range ($3.5–9.5\times10^9$/L). Besides, no significant difference was observed between the two groups in the achievement of targets. Results of Jaruratanasirikul et al recommended that 2g q8h was favorable for the critically ill patients in the early phase sepsis and septic shock.[30] However, Lertwattanachai et al show no difference between high dose of meropenem (2g q8h) and standard dosing in clinical outcomes.[41] In addition, the stability of carbapenem injection solution may contribute to the antibacterial effect.[42] Because the stability of meropenem is associated with concentrations, time and temperature,[42–44] which may partly explain why the therapeutic effect of higher dose of meropenem is not better than that of standard dose. Therefore, results of further studies have yielded conflicting conclusions regarding the optimal regimens for critically ill patients, making it difficult to determine the best approach. It is still necessary to apply TDM and individualize drug adjustment based on the predicted pharmacokinetic parameter, which may also be the best way to effectively improve the therapeutic effect of meropenem. It is clear that this study has its own limitations. First, due to the limitations of sample size and retrospective research type, our subgroup analyses may be underpowered and the extrapolation of our results is weakened. To further strengthen our conclusions, it would be beneficial to increase the sample size. Second, inconsistent sampling intervals and frequency may lead to deviation between the predicted and measured concentrations. Third, meropenem can be synergistic with other drugs to produce a good antibacterial effect in critically ill patients.[45] We have not taken into consideration the severity of patients or drug-drug interactions, which may be the covariates of meropenem pharmacokinetics.

Conclusion

It has been observed that renal function affects meropenem pharmacokinetics parameters and targets attainment. Overall, there was not comparable in most clinical outcomes especially target attainment between standard dosing group and non-standard dosing group. Due to the heterogeneity and changes of physiopathology in critically ill patients, TDM should be applied in the usage of meropenem routinely, in order to help individualize meropenem dosage.

Ethical Approval and Consent to Participate

This study has been approved by the ethics committee of Meizhou People's Hospital (2022-C-100) and complies with the Declaration of Helsinki. This study only used the patient's previous hospitalization medical information, which will not cause additional harm and risk to the patient. We will try our best to protect the rights and privacy of patients. Informed consent was waived by the ethics committee due to the nature of the retrospective study.

Consent for Publication

All authors approved the final manuscript and gave consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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