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ORIGINAL RESEARCH

Association Between Malnutrition and Multi-Drug Resistant Bacterial Infections in Neurosurgical Intensive Care Unit Patients

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Aim: Patients in the neurosurgical intensive critical unit (ICU) face high rates of malnutrition and multidrug-resistant (MDR) infections. This study aimed to investigated the correlation between malnutrition and MDR bacterial infections, aiming to offer novel strategies for preventing and controlling MDR infections from the perspective of nutritional management in clinical practice.

Methods: This retrospective cohort study analyzed 134 patients with MDR infections and 148 patients with non-MDR infections from November 2023 and May 2024 in neurosurgical ICU. MDR was defined as resistance to at least three antibiotic classes. Univariate, multivariate and correlation analyses were performed to explore the relationship between malnutrition and MDR infections.

Results: The incidence of malnutrition risk in the MDR group was significantly higher than in the non-MDR group ($P < 0.05$). After adjusting for confounding factors, malnutrition was still independently associated with an increased risk of MDR infections (OR = 2.336; 95% CI = 1.361~4.112, $P = 0.002$). Furthermore, C-reactive protein level was negatively correlated with TP (r = −0.281, $P < 0.001$), ALB (r = −0.267, $P < 0.001$), PLB (r = −0.279, $P < 0.001$), Hb (r = −0.167, $P < 0.01$) and PNI (r = −0.257, $P < 0.001$), suggesting that higher infection severity was associated with poorer nutritional status. For bacterial strains, *Acinetobacter baumannii* accounted for the largest proportion in our study.

Conclusion: Malnutrition is an independent risk factor for MDR infection in neurosurgical ICU patients. This finding highlights the need for integrated interventions targeting malnutrition in MDR prevention for neurosurgical ICU patients.

Plain Language Summary:

- Neurosurgical intensive care unit patients are highly susceptible to malnutrition and multi-drug resistant infections.
- Malnutrition independently contributes to an increased risk of developing multi-drug resistant infections.
- In critically ill patients, a strong inverse correlation exists between inflammatory markers and nutritional status.
- Early nutritional interventions are essential in the prevention and management of multi-drug resistant infections in neurosurgical intensive care unit, improving patient outcomes.

Keywords: malnutrition, bacterial infections, multi-drug resistance, neurosurgical ICU

Introduction

Hospital-acquired infections (HAIs) represent a significant complication in the neurosurgical intensive care unit (ICU), affecting approximately 63.38% of patients and contributing to prolonged hospitalization and worsened clinical outcomes.[1] The emergence of multidrug-resistant (MDR) infections further exacerbate this challenge. Approximately 44.1% of neurosurgical

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ICU patients are infected with MDR pathogens, which limit antibiotic efficacy and increase both morbidity and mortality.[2,3] Risk factors for MDR infections include device support, critical illness, immunosuppression, and inappropriate antibiotic therapy.[4] Meanwhile, due to factors such as surgical interventions, prolonged hospitalization, altered consciousness, and the need for life-support equipment, malnutrition affects up to 66.03% of neurosurgical ICU patients.[5,6] However, the extent to which malnutrition independently contributes to the risk of MDR infections in neurosurgical ICU patients remains unclear.

Malnutrition not only increases susceptibility to initial infections but also worsens disease severity and outcomes.[7] Several epidemiological studies have shown that malnourished individuals are at significantly higher risks of pneumonia, surgical site infections, and tuberculosis.[8–10] Mechanistically, nutrient deficits impair both humoral and cellular immunity by diminishing antibody synthesis and T-cell function, delay wound healing by limiting collagen deposition and angiogenesis, and weaken gut barrier integrity, thereby promoting microbial translocation.[10–12] Conversely, infections increase metabolic demands and disrupt nutrient absorption, creating a vicious cycle of worsening nutritional status and infection risk.[11] However, nutritional interventions can enhance protein synthesis, support immune cell function, and maintain the integrity of the gut barrier, thereby reducing microbial translocation and HAIs.[13] Moreover, individualized nutritional strategies are associated with shorter ICU stays and lower healthcare costs in patients with HAIs.[14]

Despite clear evidence linking malnutrition to a broad spectrum of infections, its specific role in the development and progression of MDR bacterial infections remains poorly explored. This study aims to address this knowledge gap by investigating the association between malnutrition and MDR infections, specifically focusing on neurosurgical ICU patients due to their high vulnerability to both MDR infections and malnutrition. Understanding how malnutrition exacerbates the risk and severity of MDR infections is crucial, as it may provide key theoretical support for developing targeted clinical interventions, ultimately improving outcomes for patients.

Materials and Methods

Study Population

Patients diagnosed with bacterial infections were enrolled from the neurosurgical ICU at Wuhan Union Hospital, China, between November 2023 and May 2024. The inclusion criteria were: (1) aged between 18 and 80 years; (2) neurosurgical ICU stay ≥ 7 days; (3) confirmed diagnosis of HAIs. The exclusion criteria were: (1) presence of infection or active infections prior to admission; (2) incomplete medical records; (3) non-bacterial infections (fungal, viral, or fungal-viral co-infections); (4) presence of organ failure, malignancies, or other severe comorbidities. For patients with multiple hospitalizations, only the first was included.

Definition of HAIs and MDR Infections

HAIs were infections that develop more than 48 hours after hospital admission.[15] Patients with confirmed HAIs were defined by a positive bacterial culture from a significant clinical specimen associated with clinical symptoms of infections. Lung infection was defined by clinical symptoms, radiographic evidence of inflammatory pulmonary infiltrates, and significant bacterial growth in sputum. Urinary infection was defined as the growth of bacteria in a urine sample from a patient with clinical signs of infection. Bloodstream infection was defined by the growth of bacteria in at least one blood culture or two positive blood cultures for a common skin contaminant. Central nervous system infection was defined as a positive culture of brain tissue or meninges and/or accompanied by fever (> 38°C), altered consciousness, and focal neurological signs. Surgical site infection was defined by redness, swelling, heat, pain at the incision site, and positive bacterial culture of the wound secretions.[15,16]

Antimicrobial susceptibility testing was conducted using the disk diffusion method and the Phoenix 100 automated microbiological identification system. Drug sensitivity results followed the Clinical and Laboratory Standards Institute guidelines.[17] MDR was defined as resistant to at least three antimicrobial categories.[18] Patients were divided into the MDR group and the non-MDR group based on antibiotic resistance.

The study was approved by the Ethics Committee of Wuhan Union Hospital (Approval No.0629) and conducted in accordance with the Helsinki Declaration and its amendments. Informed consent was waived by the Ethics Committee due to the retrospective nature of the study and the use of data from electronic medical records with strict confidentiality.

Nutritional Assessment

The Nutrition Risk Screening-2002 (NRS-2002) is a validated tool for assessing nutrition risk in hospitalized patients. It consists of three components: nutritional impairment, disease severity, and age.[19] The total score ranges from 0 to 7.[20] A score < 3 indicates non-nutritional risk, whereas a score ≥ 3 indicates nutritional risk. Two trained professionals assessed nutritional risk on the day that infection was diagnosed.

Clinical Data Collection

Demographic data, clinical characteristics, laboratory indicators, medication details, and clinical outcomes were collected from electronic health records. Demographic data included gender, age, and body mass index (BMI). Clinical characteristics comprised disease diagnosis, invasive treatments, consciousness disorders, surgical interventions, infection types, nutrition support (enteral nutrition (EN), parenteral nutrition (PN), or PN combined with EN) and nutrition risk. Laboratory indicators were recorded at infection diagnosis, including white blood cell count (WBC), lymphocyte count (LYM), neutrophil count (NEU), C-reactive protein level (CRP), serum total protein (TP), albumin (ALB), prealbumin (PLB), hemoglobin (Hb), prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR). Medication details focused on the use of carbapenem antibiotics, third-generation cephalosporins, total antibiotics used, antibiotic combination and duration of antibiotic therapy. Clinical outcomes included severe infections (septic shock and sepsis), length of hospital stay (from admission to discharge), survival (patients surviving without treatment-related death), and mortality (in-hospital deaths and treatment abandonment).

Data Analyses

All data were analyzed using SPSS 26.0. Continuous variables with a normal distribution were presented as mean ± standard deviation, while those with a skewed distribution were expressed as interquartile ranges. An independent sample Student's *t*-test was used for normally distributed data, and the Mann–Whitney *U*-test was applied for non-normally distributed data to compare population means. Categorical variables were expressed as percentages and analyzed using the Chi-square test. Univariate analysis was performed to compare demographic data, clinical characteristics, laboratory indicators, medication details, and outcomes between MDR and non-MDR groups. Multivariate logistic regression analyzed the association between malnutrition and MDR, with odds ratios (OR) and 95% confidence intervals (CI) calculated to assess the strength of these associations. Spearman correlation analysis examined relationships between CRP and plasma protein levels. A two-tailed p-value < 0.05 was considered statistically significant for all analyses.

Results

Characteristics of MDR and Non-MDR Group in Neurosurgical ICU Patients

Between November 2023 and May 2024, 282 patients diagnosed with bacterial infections and meeting the inclusion criteria were enrolled in this study. Patient screening followed the procedure outlined in Figure 1. Of these participants, 55.0% (155/282) were at risk of malnutrition, and 47.5% (134/282) had MDR infections. The baseline characteristics of patients in the MDR and non-MDR groups are compared in Table 1. No significant differences were observed in general demographic information ($P > 0.05$). However, the MDR group had significantly higher rates of invasive procedures, consciousness disorders, malnutritional risk, and nutritional support use ($P < 0.05$), but no difference in surgery rates ($P > 0.05$).

Regarding laboratory variables, patients in the MDR group exhibited lower levels of PNI, TP, ALB, PLB, and Hb ($P < 0.05$). No significant differences were observed in WBC, LYM, NEU, CRP, and NLR ($P > 0.05$). In terms of medication usage, the MDR patients more frequently received carbapenems and third-generation cephalosporins, used more antibiotic types, and had longer antibiotic durations ($P < 0.05$). For clinical outcomes, patients in the MDR group had significantly longer hospital stays and higher rates of severe infections ($P < 0.05$), although no significant difference in survival rate was observed ($P > 0.05$).

Univariate and Multivariate Logistic Analysis for the Risk Factor of MDR Infections

Univariate and multivariate logistic regressions were performed to identify potential risk factors for MDR infections (Table 2). In the univariate analysis, several variables were identified as potential risk factors for MDR infections, including invasive

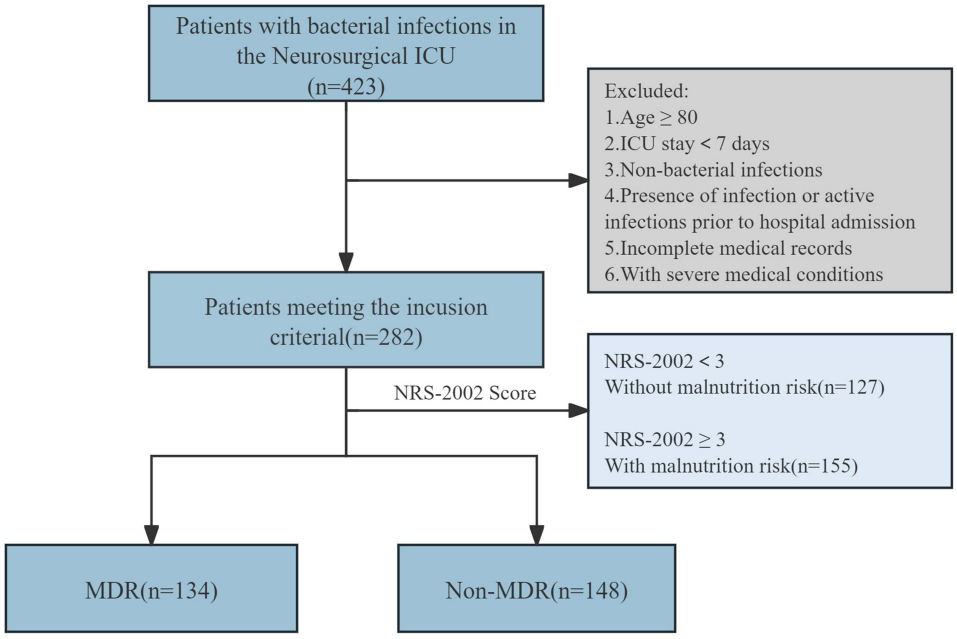

Figure 1 Flowchart of participant selection.

procedures, consciousness disorders, nutritional risk, nutrition support, use of carbapenems and third-generation cephalosporins, use of more than three types of antibiotics, antibiotic combination therapy and longer duration of antibiotic. Additionally, higher levels of TP, PLB, and Hb were identified as protective factors. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate regression analysis. The results showed that malnutrition risk (OR = 2.239, 95% CI = 1.219 ~ 4.115, $P = 0.009$), EN (OR = 5.697, 95% CI = 1.136 ~ 28.567, $P = 0.034$), and the antibiotic duration (OR = 1.092, 95% CI = 1.040 ~ 1.147, $P < 0.001$) were significantly associated with a higher risk of MDR infections.

Table 1 Demographic and Clinical Characteristics for Patients in Neurosurgical ICU

Variables	Total	MDR (N=134)	Non-MDR (N=148)	*P* Value
General information				
Age (year)	59 (49.00~66.00)	59.00 (49.00~66.75)	59.00 (49.00~66.00)	0.700
BMI	23.31 (21.07~25.66)	23.55 (21.28~25.93)	22.81 (20.76~24.97)	0.110
Gender				
Male	187 (66.30%)	93 (69.40%)	94 (63.50%)	0.296
Female	95 (33.70%)	41 (30.60%)	54 (36.50%)	
Clinical variables				
Diagnosis				0.080
Stroke	143 (50.70%)	69 (51.50%)	74 (50.00%)	
Brain injury	78 (27.70%)	43 (32.10%)	35 (23.60%)	
Intracranial space occupying	61 (21.60%)	22 (16.40%)	39 (26.40%)	
Intrusive treatments	7.00 (6.00~8.00)	7.00 (7.00~8.00)	7.00 (5.00~8.00)	<0.001
Disorders of consciousness	219 (77.70%)	114 (85.10%)	105 (70.90%)	0.004
Surgery	174 (61.70%)	76 (56.70%)	98 (66.20%)	0.101
Malnutrition Risk	155 (55.00%)	85 (63.40%)	70 (47.30%)	0.007
Nutritional support				0.006
PN	30 (10.60%)	6 (4.50%)	24 (16.20%)	
EN	13 (4.60%)	6 (4.50%)	7 (4.70%)	
PN and EN	239 (84.80%)	122 (91.00%)	117 (79.10%)	

(*Continued*)

Table 1 (Continued).

Variables	Total	MDR (N=134)	Non-MDR (N=148)	*P* Value
Laboratory variables				
WBC (× 10^9/L)	10.83 (7.89~13.90)	10.35 (7.84~13.73)	11.02 (8.10~14.09)	0.473
LYM (× 10^9/L)	0.90 (0.62~1.29)	0.89 (0.56~1.24)	0.90 (0.64~1.35)	0.260
NEU (× 10^9/L)	9.08 (6.57~12.12)	8.63 (6.11~12.26)	9.30 (6.79~12.07)	0.226
CRP (mg/L)	54.91 (23.17~106.51)	58.42 (22.85~105.71)	51.33 (24.83~107.56)	0.810
NLR	10.22 (6.12~16.49)	10.27 (6.31~16.25)	10.14 (6.00~16.73)	0.757
PNI	38.92 (33.94~43.75)	37.25 (33.18~43.08)	39.75 (35.06~44.26)	0.027
TP (g/L)	57.97±7.70	58.62±7.86	61.19±7.37	0.005
ALB (g/L)	34.20 (29.78~38.23)	32.65 (29.15~37.40)	35.40 (31.30~38.70)	0.022
PLB (g/L)	0.19±0.66	0.18±0.07	0.20±0.07	0.043
Hb (g/L)	115.51±22.45	112.19±19.43	118.51±24.55	0.017
Medications				
Usage of Carbapenems	100 (35.50%)	57 (42.50%)	43 (29.10%)	0.018
Usage of Third-generation Cephalosporins	171 (60.60%)	96 (71.60%)	75 (50.70%)	<0.001
Number of antibiotics				
<3	159 (56.40%)	52 (39.10%)	107 (72.30%)	<0.001
≥3	122 (43.40%)	81 (60.90%)	41 (27.70%)	
Antibiotic combination	199 (70.60%)	116 (86.60%)	83 (56.10%)	<0.001
Duration of antibiotic (day)	12.00 (7.00~18.00)	15.00 (11.00~21.00)	8.00 (4.00~14.75)	<0.001
Clinical outcomes				
Hospital stay (day)	15.00 (11.00~22.00)	19.00 (13.75~25.00)	12.00 (8.00~19.00)	<0.001
Severe infection	48 (17.00%)	36 (26.90%)	12 (8.10%)	<0.001
Survival	232 (83.30%)	119 (88.80%)	113 (76.40%)	0.06
Death	50 (17.70%)	15 (11.20%)	35 (23.60%)	

Notes: Categorical variables were presented with numbers (percentages). Continuous variables were presented with mean ± standard deviation or median (25th percentile-75th percentile), depending on whether the data conforms to a normal distribution. Severe infection: including septic shock and sepsis.
Abbreviations: MDR, multi-drug resistant; BMI, body mass index; PN, parenteral Nutrition; EN, enteral nutrition; WBC, white blood cell; LYM, lymphocyte; NEU, neutrophils; CRP, C-reactive protein; NLR, neutrophil lymphocyte ratio; PNI, prognostic nutritional index; TP, total protein; ALB, albumin; PLB, prealbumin; Hb, hemoglobin.

Table 2 Univariate and Multivariate Logistic Regression Analysis for the Risk Factors for MDR

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
General information				
Age (year)	0.966(0.979~1.014)	0.686	–	–
BMI	1.038(0.970~1.111)	0.278	–	–
Female	Ref	Ref	–	–
Male	1.303(0.793~2.142)	0.297	–	–
Clinical variables				
Diagnosis				
Stroke	Ref	Ref	–	–
Brain injury	1.318(0.757~2.292)	0.329	–	–
Intracranial space occupying	0.605(0.326~1.121)	0.110	–	–
Intrusive treatments	1.357(1.172~1.571)	<0.001	1.010(0.832~1.228)	0.917
Consciousness disorders				
No	Ref	Ref	Ref	Ref
Yes	2.334(1.290~4.224)	0.005	1.834(0.872~3.858)	0.110

(*Continued*)

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Table 2 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Surgery				
No	Ref	Ref	–	–
Yes	0.669(0.413~1.083)	0.102	–	–
Malnutrition Risk				
No	Ref	Ref	Ref	Ref
Yes	1.933(1.199~3.115)	0.007	2.239(1.219~4.115)	0.009
Nutritional support				
PN	Ref	Ref	Ref	Ref
EN	3.429(0.837~14.049)	0.837	5.697(1.136~28.567)	0.034
PN and EN	4.171(1.646~10.570)	0.003	1.703(0.563~5.149)	0.346
Laboratory variables				
WBC (× 10^9/L)	1.000(0.959~1.043)	1.000	–	–
LYM (× 10^9/L)	0.847(0.590~1.216)	0.369	–	–
NEU (× 10^9/L)	0.988(0.946~1.031)	0.569	–	–
CRP (mg/L)	1.000(0.997~1.004)	0.828	–	–
NLR	1.012(0.993~1.032)	0.221	–	–
PNI	0.974(0.943~1.006)	0.108	–	–
TP (g/L)	0.956(0.927~0.987)	0.006	0.976(0.934~1.020)	0.276
ALB (g/L)	0.973(0.937~1.011)	0.158	–	–
PLB (g/L)	0.027(0.01~0.917)	0.045	0.083(0.001~9.404)	0.303
Hb (g/L)	0.987(0.977~0.998)	0.019	0.998(0.984~1.013)	0.828
Medications				
Usage of Carbapenems				
No	Ref	Ref	Ref	Ref
Yes	1.808(1.104~2.960)	0.019	0.782(0.396~1.543)	0.478
Usage of Third-generation Cephalosporins				
No	Ref	Ref	Ref	Ref
Yes	2.459(1.499~4.034)	<0.001	1.204(0.621~2.333)	0.582
Number of antibiotics				
<3	Ref	Ref	Ref	Ref
≥3	4.065(2.463~6.708)	<0.001	1.822(0.874~3.798)	0.109
Antibiotic combination				
No	Ref	Ref	Ref	Ref
Yes	5.003(2.764~9.057)	<0.001	2.187(0.967~4.948)	0.060
Duration of antibiotic (day)	1.126(1.085~1.169)	<0.001	1.092(1.040~1.147)	<0.001

Abbreviations: BMI, body mass index; PN, parenteral Nutrition; EN, enteral nutrition; WBC, white blood cell; LYM, lymphocyte; NEU, Neutrophils; CRP, C-reactive protein; NLR, neutrophil lymphocyte ratio; PNI, prognostic nutritional index; TP, total protein; ALB, albumin; PLB, prealbumin; Hb, hemoglobin; Ref, reference.

To further explore the relationship between malnutrition risk and MDR infections, we conducted multivariate logistic regression, controlling for potential confounding factors. Variance inflation factors for all variables were less than 10. The results are presented in Table 3. In the unadjusted model, the prevalence of MDR infection was significantly associated with malnutrition risk (OR = 1.933, 95% CI = 1.199 ~ 3.155, $P = 0.007$). After adjusting for key demographic and clinical variables such as gender, age, BMI, consciousness disorders, diagnosis, surgery, nutritional support, and invasive treatments in Model 1, malnutrition risk remained an independent risk factor for MDR infections (OR = 1.810, 95% CI = 1.093 ~ 2.997, $P = 0.021$). In Model 2, additional adjustments were made for laboratory variables, including WBC, NEU, CRP, NLR, PNI, TP, ALB, PLB, and Hb. The association between malnutrition risk and MDR infections remained statistically significant (OR = 1.727, 95% CI = 1.037 ~ 2.876, $P = 0.036$). In the fully adjusted Model 3, which included all variables, malnutrition was a strong and independent risk factor for MDR infections (OR = 2.336, 95% CI = 1.361 ~ 4.112, $P = 0.002$).

Table 3 Association between Malnutrition Risk and MDR

Variables	OR (95% CI)			
	Crude	Model 1	Model 2	Model 3
Without Malnutrition risk	1	1	1	1
Malnutrition risk	1.933 (1.199~3.155)	1.810 (1.093~2.997)	1.727 (1.037~2.876)	2.336(1.361~4.112)
β	0.659	0.593	0.547	0.861
SE	0.243	0.257	0.260	0.282
p-value	0.007	0.021	0.036	0.002

Notes: Crude: no adjustment. Model 1: adjust for gender, age, BMI, disorders of consciousness, diagnosis, surgery, nutrition support, intrusive operations. Model 2: adjusted for the same variables as Model 1 as well as WBC, NEU, CRP, NLR, PNI, TP, ALB, PLB, Hb. Model 3: adjusted for the same variables as Model 2 as well as duration of antibiotic, Carbapenems, Third-generation Cephalosporins, number of antibiotics, antibiotic combination.

Correlations of CPR with TP, ALB, PLB, Hb, and PNI

To investigate the correlation between CRP and TP, ALB, PLB, Hb, and PNI, we conducted Spearman correlation analyses. As shown in Figure 2, CRP level was inversely correlated with TP ($r = -0.281$, $P < 0.001$, Figure 2A), ALB ($r = -0.267$, $P < 0.001$, Figure 2B), PLB ($r = -0.279$, $P < 0.001$, Figure 2C), Hb ($r = -0.167$, $P < 0.01$, Figure 2D), and PNI ($r = -0.257$, $P < 0.001$, Figure 2E). These findings suggest that higher level of inflammation, indicated by elevated CRP, are associated with lower nutritional markers, supporting the positive link between infection and nutrition status.

Bacterial Detection Distribution

A total of 424 strains of bacteria were detected from qualified clinical specimens of 282 patients. In the MDR and malnutrition risk group, *Acinetobacter baumannii* (45.6%), *Klebsiella pneumoniae* (16.9%), and *Pseudomonas aeruginosa* (15.4%) were the most frequently detected pathogens. For the MDR and without malnutrition risk group, the most commonly isolated bacteria were *Acinetobacter baumannii* (41.6%), *Escherichia coli* (18.1%), and *Klebsiella pneumoniae* (16.9%). In the group

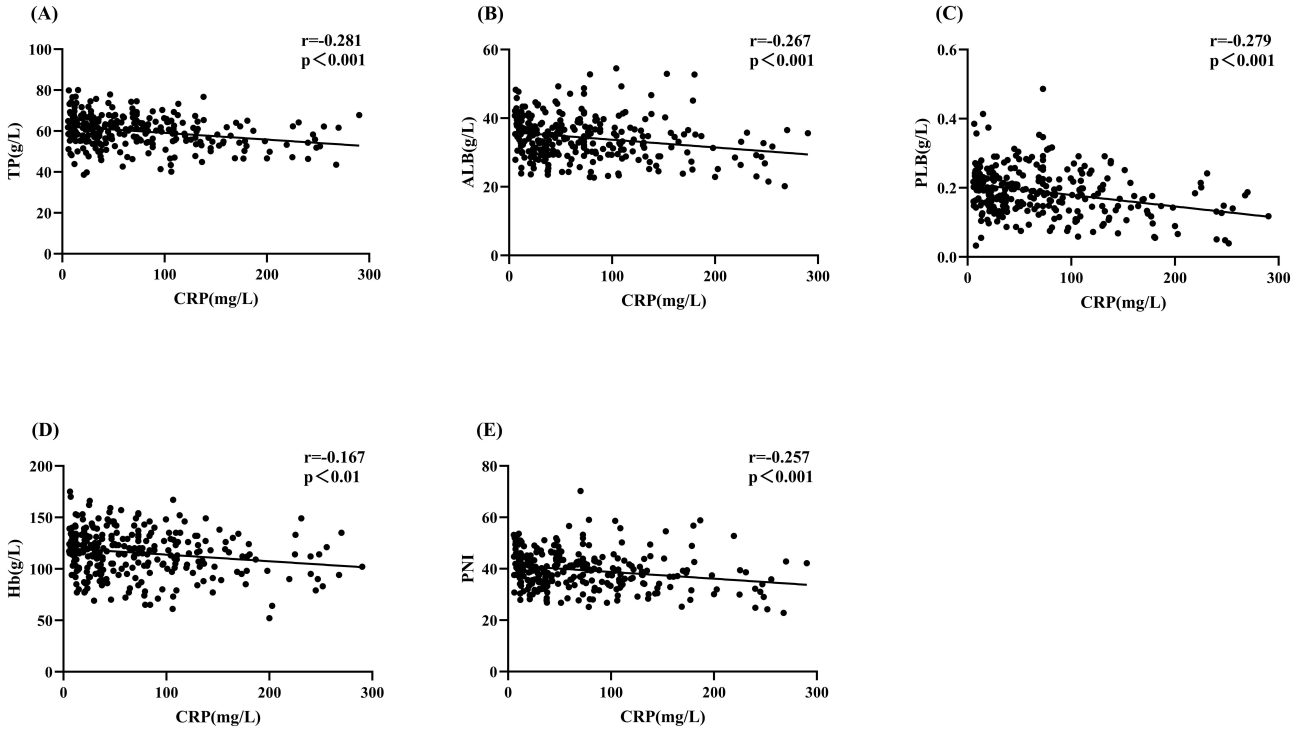

Figure 2 Correlations of CRP with plasma TP (**A**)/ALB (**B**)/ PLB (**C**)/Hb (**D**)/PNI (**E**) of patients with bacterial infections.
Abbreviations: CRP, C-reactive protein; TP, total protein; ALB, albumin; PLB, prealbumin; Hb, hemoglobin; PNI, prognostic nutritional index.

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of non-MDR and malnutrition risk, *Klebsiella pneumoniae* (38.2%), *Escherichia coli* (18.6%), and *Pseudomonas aeruginosa* (16.7%) were the most frequently isolated bacteria. In the non-MDR and without malnutrition risk group, *Klebsiella pneumoniae* (33.0%), *Escherichia coli* (24.7%) and *Acinetobacter baumannii* (19.3%) were the most frequently detected pathogens (Figure 3A). Among MDR isolates, Carbapenem-resistant *Acinetobacter baumannii* accounted for the largest proportion in both malnutrition group and without malnutrition group. Compared with the MDR without malnutrition risk group, the MDR with malnutrition risk group had higher proportions of carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa*, but lower proportions of carbapenem-resistant *Enterobacterales*, methicillin-resistant *Staphylococcus aureus*, and extended-spectrum *β*-lactamase-producing strains. However, none of these differences were statistically significant ($P > 0.05$) (Figure 3B).

The lung was identified as the most common site of infections. However, the four groups had no statistically significant difference in the infection sites (Figure 3C). A higher prevalence of multiple bacterial co-infections was observed in the MDR and malnutrition risk group, with 52.9% of clinical specimens showing co-infection (Figure 3D). It suggested that multiple bacterial infections were common, particularly among patients with MDR infections and malnutrition.

Acinetobacter baumannii exhibited a high level of antimicrobial resistance, with resistance rates more than 60% for all commonly used antibiotics. For *Pseudomonas aeruginosa*, the resistance rate to imipenem was 33.3%, while its resistance to other antibiotics remained below 30%. In the case of *Klebsiella pneumoniae*, the resistance rates for

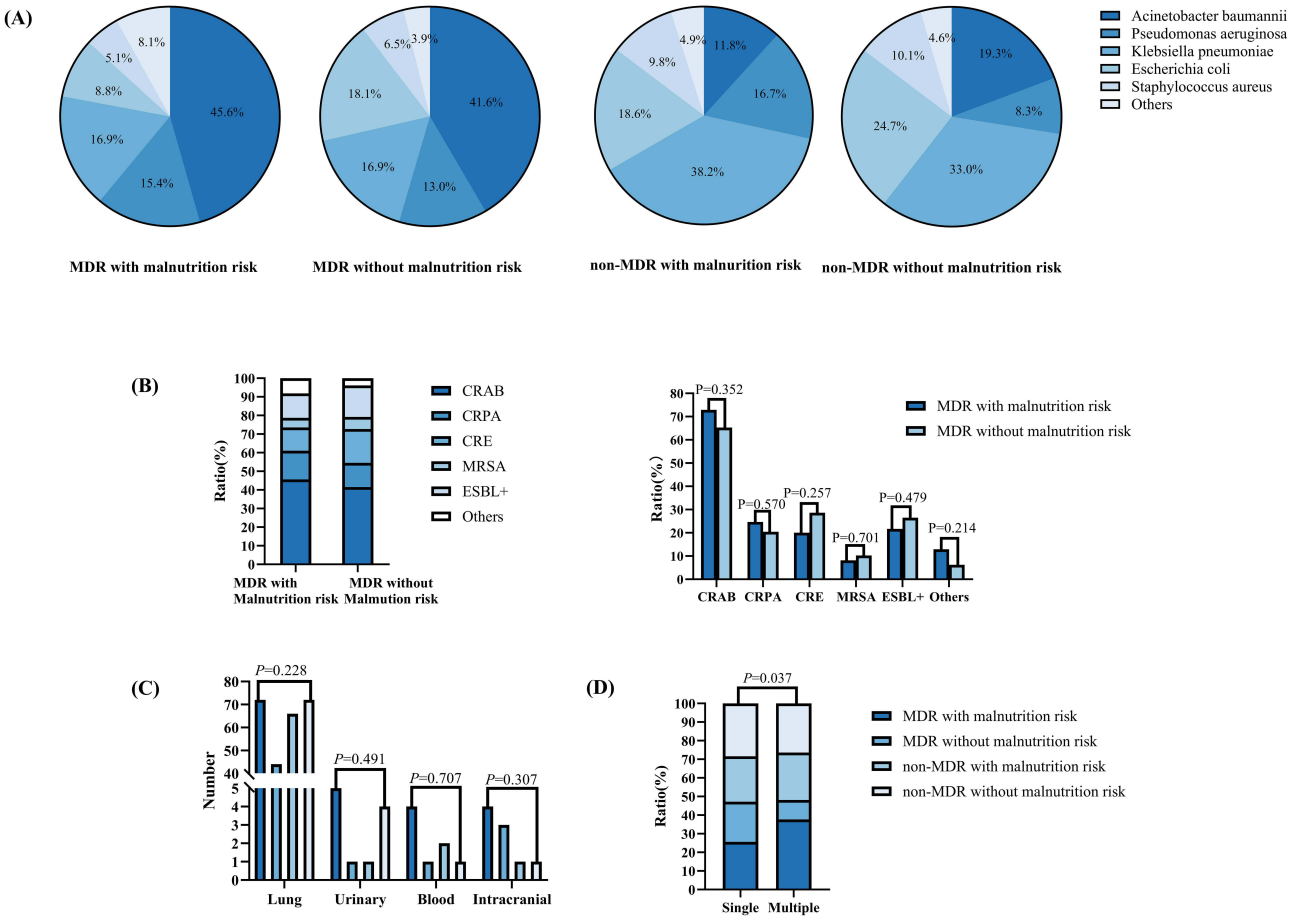

Figure 3 Bacterial and infection distribution. (**A**) proportion of bacteria in MDR with malnutrition risk group, MDR without malnutrition risk group, non-MDR with malnutrition risk group, and non-MDR without malnutrition risk group. (**B**) distribution of MDR strains in MDR with malnutrition group and MDR without malnutrition group. (**C**) distribution of the number of bacterial infections in MDR with malnutrition risk group, MDR without malnutrition risk group, non-MDR with malnutrition risk group, and non-MDR without malnutrition risk group (**D**) comparison of the number of infections in MDR with malnutrition risk group, MDR without malnutrition risk group, non-MDR with malnutrition risk group, and non-MDR without malnutrition risk group.

Abbreviations: MDR, multi-drug resistant; CRAB, Carbapenem-resistant *Acinetobacter baumannii*; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CRE, Carbapenem-resistant *Enterobacterales*; MRSA, Methicillin-resistant *Staphylococcus aureus*; ESBL+, Extended-spectrum *β*-lactamase-producing strains.

amikacin and imipenem were 21.6% and 29.7%, with the most resistance rates ranging from 30% to 40%. *Escherichia coli* showed low resistance rates to imipenem, meropenem, and amikacin, while its resistance to other antibiotics rangeed from 30% to 50%. As for *Staphylococcus aureus*, the resistance to penicillin G was notably high at 90.9%, while its resistance to erythromycin and cloxacillin were 54.5% and 42.4%, respectively. However, its resistance to minocycline was 0.3% (Table S1).

Subgroup Analysis of Characteristics in the Survival Group

Among 119 surviving MDR patients and 113 non-MDR survivors, subgroup analysis (Table 4) showed no demographic differences. However, clinical variables such as the rate of consciousness disorders, invasive treatments, malnutrition risk, and severe infection were significantly higher in the MDR group ($P < 0.05$). There were no significant differences between the groups regarding diagnosis, surgery, or nutritional support. Regarding laboratory variables, patients in the

Table 4 Subgroup Analysis of Survival Group in Neurosurgical ICU

Variables	MDR (N=119)	Non-MDR (N=113)	*P* Value
General information			
Age (year)	59.00 (48.00~65.00)	59.00 (49.50~67.00)	0.442
BMI	23.44±3.01	23.15±3.65	0.507
Male	80 (67.20%)	70 (61.90%)	0.400
Clinical variables			
Diagnosis			
Stroke	62 (52.10%)	63 (55.80%)	0.261
Brain injury	38 (31.9%)	26 (23.00%)	
Intracranial space occupying	19 (16.00%)	24 (21.20%)	
Intrusive treatments	8.00 (7.00~9.00)	7.00 (5.50~8.00)	0.001
Consciousness disorders	101 (84.90%)	84 (74.30%)	0.046
Surgery	65 (54.60%)	74 (65.50%)	0.091
Malnutrition Risk	76 (63.90%)	54 (47.80%)	0.014
Nutritional support			
PN	5 (4.20%)	14 (12.50%)	0.069
EN	6 (5.00%)	4 (3.50%)	
PN and EN	108 (90.80%)	95 (84.10%)	
Laboratory variables			
WBC (× 10^9/L)	10.34 (7.86~13.78)	11.06 (7.95~14.16)	0.619
LYM (× 10^9/L)	0.92 (0.63~1.25)	0.85 (0.64~1.30)	0.801
NEU (× 10^9/L)	8.69 (6.21~12.28)	9.60 (7.00~12.17)	0.236
CRP (mg/L)	53.39 (21.60~102.50)	49.80 (23.05~106.26)	0.958
NLR	9.99 (6.14~15.38)	10.26 (6.07~18.32)	0.833
PNI	37.70 (33.50~43.30)	39.65 (35.53~43.88)	0.124
TP (g/L)	59.05±7.78	61.21±6.97	0.028
ALB (g/L)	32.90 (29.40~38.00)	35.30 (31.35~38.20)	0.160
PLB (g/L)	0.18±0.07	0.20±0.06	0.048
Hb (g/L)	113.48±19.03	119.62±23.42	0.029
Medications			
Usage of Carbapenems	50 (42.00%)	33 (29.20%)	0.042
Usage of Third-generation Cephalosporins	87 (73.10%)	55 (48.70%)	<0.001
Number of antibiotics			
<3	47 (39.80%)	83 (73.50%)	<0.001
≥3	71 (60.20%)	30 (26.50%)	
Antibiotic combination	102 (86.40%)	63 (55.8%)	<0.001
Duration of antibiotic (day)	16.00 (12.00~22.00)	10.00 (4.50~15.50)	<0.001

(*Continued*)

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Table 4 (Continued).

Variables	MDR (N=119)	Non-MDR (N=113)	*P* Value
Clinical outcomes			
Hospital stay (day)	20.00 (14.00~25.00)	13.00 (8.00~20.00)	<0.001
Severe infection	29 (24.40%)	7 (6.20%)	<0.001

Notes: Categorical variables were presented with numbers (percentages). Continuous variables were presented with mean ± standard deviation or median (25th percentile-75th percentile), depending on whether the data conforms to a normal distribution. Severe infection: including septic shock and sepsis.

Abbreviations: MDR, multi-drug resistant; BMI, body mass index; PN, parenteral Nutrition; EN, enteral nutrition; WBC, white blood cell; LYM, lymphocyte; NEU, Neutrophils; CRP, C-reactive protein; NLR, neutrophil lymphocyte ratio; PNI, prognostic nutritional index; TP, total protein; ALB, albumin; PLB, prealbumin; Hb, Hemoglobin.

Table 5 Association between Malnutrition Risk and MDR in Survival Group

	OR (95% CI)			
	Crude	Model 1	Model 2	Model 3
Without Malnutrition risk	1	1	1	1
Malnutrition risk	1.931 (1.142~3.266)	1.784 (1.028~3.095)	1.784 (1.028~3.095)	2.545 (1.391~4.656)
β	0.658	0.579	0.579	0.934
SE	0.268	0.281	0.281	0.308
p for trend	0.014	0.040	0.040	0.002

Notes: Crude: no adjustment. Model 1: adjust for gender, age, BMI, consciousness disorders, diagnosis, surgery, nutrition support, Intrusive operations. Model 2: adjusted for the same variables as Model 1 as well as WBC, NEU, CRP, NLR, PNI, TP, ALB, PLB, Hb. Model 3: adjusted for the same variables as Model 2 as well as Duration of antibiotic, Carbapenems, Third-generation Cephalosporins, Number of antibiotics, Antibiotic combination.

MDR group exhibited significantly lower levels of, TP, PLB, and Hb ($P < 0.05$). However, no significant differences were found for WBC, NEU, LYM, CRP, NLR, PNI or ALB. In terms of medication use, significant differences were observed between the two groups regarding the use of carbapenems, third-generation cephalosporins, the number of antibiotics, antibiotic combination and the duration of antibiotic therapy ($P < 0.05$). Clinical outcomes showed that the length of hospital stay was significantly longer in the MDR group compared to the non-MDR group ($P < 0.05$).

Multivariate logistic regression was performed to explore the relationship between malnutrition risk and MDR infections, as shown in Table 5. All variables showed no significant multicollinearity, with variance inflation factors less than 10. In the unadjusted model, malnutrition risk was positively associated with MDR infections, yielding an OR of 1.931 (95% CI = 1.142 ~ 3.266, $P = 0.014$). After adjusting for clinical characteristics such as gender, age, BMI, consciousness disorders, diagnosis, surgery, nutritional support, and invasive treatments in Model 1, the association remained significant, with an OR of 1.784 (95% CI = 1.028 ~ 3.095, $P = 0.040$). In Model 2, with additional adjustments for WBC, NEU, CRP, NLR, PNI, TP, ALB, PLB, and Hb, the association remained statistically significant with an OR of 1.784 (95% CI = 1.028 ~ 3.095, $P = 0.040$). In the fully adjusted Model 3, the OR for MDR infections was 2.545 (95% CI = 1.391 ~ 4.656, $P = 0.002$), demonstrating a strong and significant relationship between malnutrition risk and MDR infections.

Discussion

Patients in the neurosurgical ICU are particularly vulnerable to both malnutrition and MDR infections due to the combined impact of neurological impairment, prolonged mechanical ventilation, and complex postoperative care. While previous research has linked malnutrition to infection risk in general populations, limited evidence exists regarding its specific association with MDR infections in neurosurgical ICU patients. To our knowledge, this is the first study to systematically investigate the relationship between malnutrition risk and MDR infections in this high risk population. Our findings not only identify malnutrition as an independent and modifiable risk factor for MDR infections, but also suggest that nutritional support could serve as a novel strategy for controlling MDR infections in neurosurgical ICU settings.

This study found that malnutrition is independently associated with an increased risk of MDR infections in neurosurgical ICU patients. This aligns with previous evidence linking malnutrition to a higher risk of various infections. For instance, malnutrition risk independently increased the risk of stroke-associated pneumonia in stroke patients.[8] Additionally, a meta-analysis reported that malnutrition increaseed the risk of surgical site infections by 1.64 times.[21] Another study found that malnutrition not only heightened susceptibility to tuberculosis but also worsened treatment outcomes, including treatment failure, loss of follow-up, and death.[22] These results consistently indicate that malnutrition is a critical risk factor for both common and MDR infections.

The relationship between malnutrition and MDR infections is complex and can be explained by several mechanisms. First, malnutrition is a major cause of nutritionally acquired immune deficiency syndrome, which weakens both adaptive and innate immune responses.[11,23,24] This weakened immune increases vulnerability to infections, particularly those caused by MDR pathogens. Second, MDR bacteria exhibit greater resistance to conventional disinfectants and antimicrobial agents compared with non-MDR bacteria, making them more difficult to eradicate in hospital environments.[25,26] Consequently, patients with weakened immune systems are more susceptible to MDR infections. Third, malnutrition impairs tissue repair and regeneration, prolonging wound healing and creating a favorable environment for MDR bacteria.[27] Additionally, poor nutritional status affects drug pharmacokinetics, including distribution, absorption, plasma binding, activation, and clearance.[28] This may result in higher doses or longer durations of antibiotic treatment, further increasing the risk of developing MDR infections.

The relationship between malnutrition and MDR infections is bidirectional. Malnutrition weakens immune functions, increasing the risk and severity of MDR infections. On the other hand, MDR infections exacerbate malnutrition by increasing metabolic demands, leading to hypermetabolism and hypercatabolism, which rapidly deplete nutritional reserves. This vicious cycle worsens both infections and overall health, complicating recovery efforts.[29] The heightened metabolic demand, reduced nutrient absorption and utilization due to infections further worsen malnutrition. Breaking this cycle requires an integrated approach combining nutritional rehabilitation and strict infection control measures. In neurosurgical ICU, EN support is a critical source of nutrition, but infections can impair gastrointestinal function, reducing tolerance to EN and contributing to malnutrition. The interplay between malnutrition and MDR infections amplifies the burden on ICU recovery, complicating physical rehabilitation and negatively affecting patient outcomes. Understanding this complex relationship is essential for optimizing treatment strategies and improving recovery. Proactive nutritional interventions, alongside robust infection management, are critical to improving survival rates and reducing the complications associated with MDR infections in critically ill neurosurgical patients.

The negative correlation between inflammation and malnutrition indicators may provide valuable insights into the relationship between malnutrition and the risk of MDR infections. In our study, CRP levels were inversely associated with TP, ALB, PLB, Hb, and PNI. Several studies have also demonstrated that inflammatory biomarkers, such as the systemic immune-inflammation index, WBC, NLR, NEU, LYM, and CRP, are strongly associated with nutritional indicators such as the controlling nutritional status score, geriatric nutritional risk index, PNI, and ALB.[8] This inverse relationship suggests that poor nutritional status, as indicated by these markers, may reflect heightened inflammatory and metabolic responses, contributing to the progression of MDR infections. Elevated CRP level, a marker of systemic inflammation, indicates the body's response to infection or tissue injury, suppressing appetite, impairing nutrient absorption, and leading to muscle wasting and a decline in protein reserves.[30] This chronic inflammatory state not only worsens malnutrition but also weakens the immune system, increasing susceptibility to MDR infections.[31] These findings underscore the complex relationship between inflammation, malnutrition, and immune dysfunction, in which elevated inflammatory markers often coincide with declines in nutritional status, thereby compounding the risk of severe infections, including those caused by MDR pathogens.

The distribution of MDR pathogens in relation to malnutrition presents a complex and interconnected dynamic that probably influences patient outcomes. In our study, *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas aeruginosa* emerged as the predominant MDR pathogens. These bacteria are parts of ESKAPE group, which are responsible for a significant proportion of antibiotic-resistant infections in clinical medicine.[32,33] These pathogens are particularly challenging to treat due to their ability to acquire resistance mechanisms, resulting in conventional antibiotic therapies being ineffective. *Acinetobacter baumannii* thrives in ICU environments where patients are highly vulnerable due to invasive procedures, prolonged mechanical ventilation, and the extensive use of broad-spectrum antibiotics. Similarly, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are notorious for resisting multiple antibiotics and colonizing tissues that are already compromised. Notably, *Pseudomonas aeruginosa* is highly adept at forming biofilms, which are complex

aggregations of bacteria that adhere to surfaces and provide a protective barrier, making the bacteria even more resistant to antibiotic treatments. Malnutrition, often associated with chronic inflammation, creates an environment conducive to the proliferation of MDR pathogens. Inflammatory responses in malnourished patients can promote bacterial growth and enhance biofilm formation, particularly in pathogens like *Pseudomonas aeruginosa*, contributing to increased antibiotic resistance.[26,34] The biofilms formed by these pathogens act as protective barriers, shielding bacterial colonies from immune defenses and antibiotic therapies, thereby prolonging infections and increasing morbidity and mortality.

Given the role of malnutrition in increasing the risk of MDR infections, nutritional intervention is essential and should be integrated into MDR infections prevention strategies. Screening for nutritional risk within the first 24~48 hours of admission, with validated tools such as the NRS-2002 or the NUTRIC score enables timely identification of risk patients.[35] For hemodynamically stable patients without feeding contraindications, EN should be started within 72 hours. For severely malnourished patients with enteral feeding contraindications, early PN is recommended.[36] Immune-modulating formulas enriched with omega-3 fatty acids, glutamine, probiotics, vitamins, and selenium have also been shown to enhance host immunity and may contribute to reducing infection risk.[37] Because both nutritional status and infection are dynamic and can change rapidly, nutritional status and infections should be reassessed every 3~5 days to guide adjustments in nutrition support.[36] However, insufficient attention to malnutrition and limited resources may limit effective implementation in clinical practice. Thus, multidisciplinary teams and artificial intelligence-based risk alert systems are essential for effective and timely care of malnutrition and MDR infections.

Limitations

This study has several limitations. First, although it is a single-center study conducted in Wuhan, China, the data were collected from both the primary and satellite campuses. Second, while this is a retrospective study, we made efforts to control potential biases through strict inclusion and exclusion criteria, standardized data collection procedures, and multivariate statistical methods. We are conducting large number, multicenter, and prospective studies to validate our findings in our ongoing study. Third, nutritional assessment was based on NRS-2002 and serum protein levels. While the NRS-2002 is a globally recognized clinical tool for evaluating nutritional risk, the Subjective Global Assessment and the Global Leadership Initiative on Malnutrition are increasingly adopted in clinical practice. Therefore, we intend to conduct longitudinal studies incorporating these assessment methodologies. Fourth, this study can only identify the association between malnutrition and MDR infections. We are currently conducting a prospective study to further explore the causal relationship between malnutrition and MDR infections.

Conclusion

In conclusion, our study revealed that malnutrition risk increases the risk of MDR infections in neurosurgical ICU patients. This finding provides new insights into the prevention and treatment of MDR infections. However, the retrospective nature of our study limits to establish potential causal and reverse causality relationship. Therefore, prospective interventional trials examining the impact of early nutritional support on infection risk are essential to validate these findings and further guide clinical practice.

Abbreviations

ICU, intensive care unit; MDR, multi-drug resistant; HAIs, hospital-acquired infections; NRS-2002, Nutrition Risk Screening-2002; BMI, body mass index; WBC, white blood cell; LYM, lymphocyte; NEU, Neutrophils; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PNI, prognostic nutritional index; TP, total protein; ALB, albumin; PLB, prealbumin; Hb, hemoglobin; PN, parenteral nutrition; EN, enteral nutrition; ESBL, Extended-spectrum beta-lactamases; OR, odds ratios; CI, confidence intervals.

Data Sharing Statement

The data used in this study is restricted through public channels due to privacy protection and ethical standards. Requests to access the data should be directed to the corresponding author (yan_ouyang@hust.edu.cn, 13986213577@163.com).

Ethics Statement

The study was approved by the Ethics Committee of Union Hospital, Tongji Medical Collage, Huazhong University of Science and Technology, China (Approval No.0629) and complies with the Helsinki Declaration. Informed consent was waived by the Ethics Committee due to the retrospective nature of the study and the use of data from electronic medical records with strict confidentiality.

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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.

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Disclosure

The authors declare that there are no conflicts of interest.

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