

# A Meta-analysis of Mortality Factors in Patients with *Klebsiella Pneumoniae* Bloodstream Infection

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## Abstract

**Objective:** To systematically analyze the risk factors for bloodstream infections (BSI) of *Klebsiella pneumoniae* (KP) and its adverse prognosis (death), and provide theoretical basis for improving clinical prevention and control efficiency and reducing mortality. **Methods:** The literatures related to KP BSI risk factors and death risk factors were searched in CNKI, Wanfang, VIP, PubMed and Cochrane databases. Relevant literatures were screened according to inclusion and exclusion criteria, and the quality evaluation and data extraction were carried out for the finally included literatures. Meta-analysis was conducted by STATA12.0 software. **Results:** A total of 9 literatures were included with a total sample size of 2014, all of which were retrospective studies with NOS scores of 7-9. Meta analysis showed that: the history of hospitalization, history of ICU stay, high blood pressure, heart disease, kidney disease, lung disease, liver abscess, hypoalbuminemia, hemodialysis, mechanical ventilation, deep venipuncture, indwelling gastric tube, parenteral nutrition, placing a urinary catheter use radiotherapy/chemotherapy, hormone and immune inhibitor use, antibiotics (beta lactam, carbon green alkene, quinolone, for ring element, cephalosporins) the use of the difference between groups was statistically significant ( $P < 0.05$ ). Publication bias showed that ICU admission history, hypertension, and malignant tumors were biased. After the one-way study was adopted, ICU admission history and hypertension had no significant bias, which was accepted. **Conclusion:** the history of hospitalization, history of ICU stay, high blood pressure, heart disease, kidney disease, lung disease, liver abscess, hypoalbuminemia, hemodialysis, mechanical ventilation, deep venipuncture, indwelling gastric tube, parenteral nutrition, placing a urinary catheter use radiotherapy/chemotherapy, hormone and immune inhibitor use, antibiotics (beta lactam, carbon green alkene, quinolone, for ring element, cephalosporins) the use of KP is the major risk factors of death in patients with bloodstream infections.

## Keywords

***Klebsiella Pneumoniae*; Bloodstream Infection; Death Factors; Meta Analysis.**

## 1. Introduction

*Klebsiella pneumoniae* (KP) is a common cause of nosocomial infection. In China, the infection rate of *Klebsiella pneumoniae* is second only to *Escherichia coli* [1-4]. The fatality rate of bloodstream infection caused by *Klebsiella pneumoniae* is high [5-7], has become a thorny problem faced by hospitals around the world. This paper extracted, summarized and analyzed the data of 9 relevant studies to explore the risk factors of death caused by *Klebsiella pneumoniae* bloodstream infection and provide more data support for clinical prevention of bloodstream infection caused by related factors.

## 2. Materials and Methods

### 2.1. Literature Retrieval

Computer retrieval CNKI, WANFANG, VIP, PubMed and the Cochrane library database built in October 2020, the publicly literature, the English term "Klebsiella pneumoniae" "bloodstream infection" "risk factors" English database search, search by Chinese word "Klebsiella pneumoniae" bloodstream infections, "" Chinese database search" risk factors ", and the references in the literature retrieval, to enlarge the scope of literature retrieval, Screen for more studies that meet the inclusion criteria.

### 2.2. Inclusion and Exclusion Criteria

Inclusion criteria: (1) Published studies that were case-control studies or cohort studies; (2) The subjects were included in all departments of the hospital, rather than local departments; (3) The outcome indexes were death or not, and the case group/control group were set as KP BSI survival group and KP BSI death group according to the outcome of the study object;

Exclusion criteria: (1) Pediatric KP BSI study; (2) The research objects were only distributed in local hospital departments, such as THE STUDY of ICU patients KP BSI; (3) Studies with disease outcome indicators inconsistent with this analysis; (4) The strains infected in the study were subgroups of KPC strains, such as blaKPC strain or high virulence KPC strain, etc. (5) Research objects were selected from areas outside the hospital scope, such as community infection, etc. (6) Review, case reports, case reports and other literature; (7) Repeated literature, unable to obtain the full text of the literature; (8) Read the abstract or the full text of the literature is not consistent with the analysis; (9) Literature with low quality score.

### 2.3. Literature Screening, Quality Evaluation and Collection

According to the above retrieval methods, related literatures of October 2020 were searched in each Chinese or English database to form preliminary screening literatures. Irrelevant or inconsistent literatures were removed according to inclusion and exclusion criteria; Forming secondary screening literature; Newcastle-ottawa (NOS) scale was used [17] Evaluate the quality of the literature obtained by the secondary screening, remove the low-quality literature, and form the final literature to be collected.

### 2.4. Data Extraction

### 2.5. Statistical Analysis

## 3. The Results

### 3.1. Literature Retrieval Results

According to the above retrieval methods, a total of 684 related literatures were obtained, and 638 irrelevant literatures were removed by reading abstracts and selected articles. Sixteen duplicate literatures were removed by reading title, author and publication year. Sixteen pediatric studies, reviews, case reports, case reports and literatures whose full text could not be obtained were removed. Through detailed reading of the full text, 5 articles inconsistent with the inclusion criteria of this study were removed. Finally, there were 9 relevant articles [8-16] included in this study, the specific screening process is shown in Figure 1. Among the included articles, 1 was 9 points at NOS, 5 were 8 points at NOS, and 3 were 7 points at NOS. The overall quality of the articles was high.

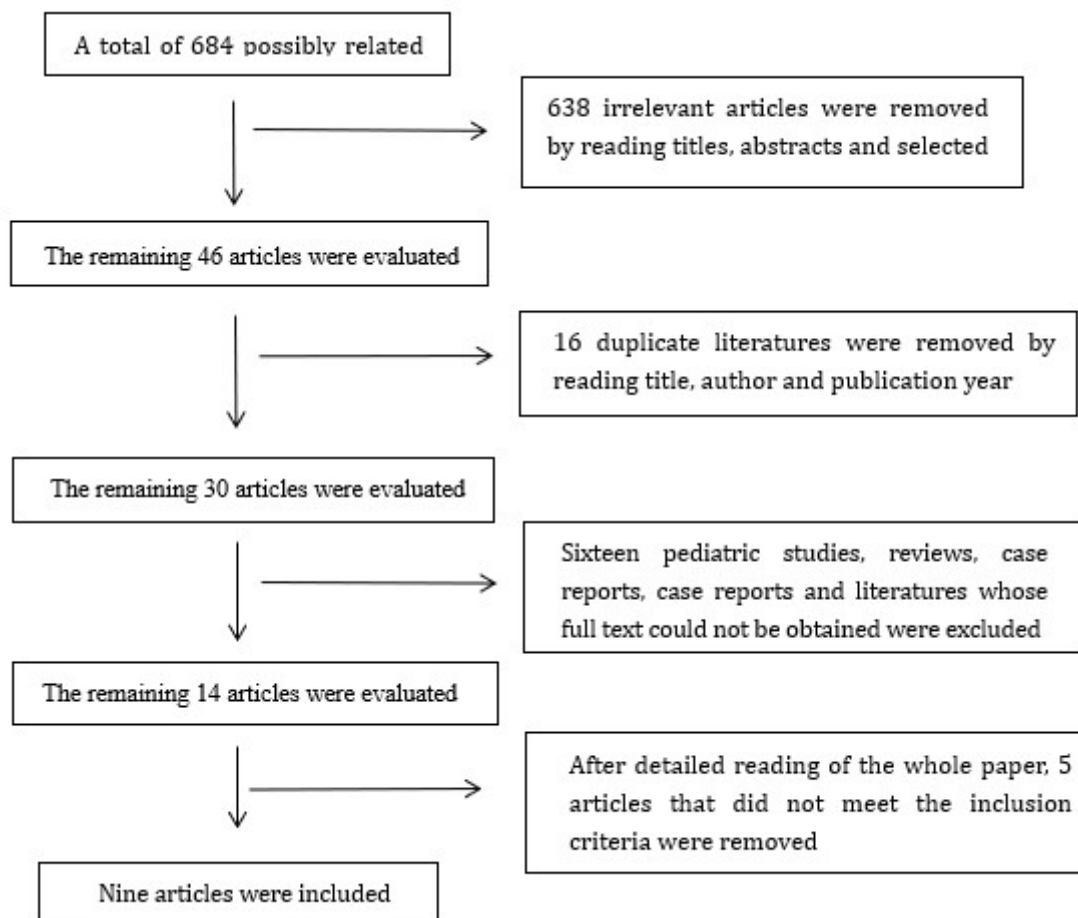


Figure 1. Flow chart of literature screening

### 3.2. Basic Characteristics and Quality Evaluation of the Included Literature (see Table 1)

Table 1. Basic features included in the meta-analysis of risk factors for death from KP bloodstream infection

The author	year	The research type	Time of case inclusion	Study sites	Survival/death group	Number of males (survival/death)	Mean age (survival/death)	NOS score
Ting-ting xiao	2018	retrospective	2013/1-2015/12	The First Affiliated Hospital of Zhejiang University	292/78	202/57	58.5 +/- 16.6/58.6-15.8 <sup>a</sup>	9
Shen Ziyang	2020	retrospective	2014/5-2019/4	The Second Affiliated Hospital of Nanjing Medical University	62/28	42/22	38/23 <sup>c</sup>	8
Yuanyuan Li	2020	retrospective	2014/1-2019/6	the second hospital of Hebei Medical University	371/121	233/72	56/63	8
Wei Xu Peng	2020	retrospective	2018/1-2018/12	Henan Provincial People's Hospital	71/46	46/27	53.1 +/- 16.1/59.1-13.0 <sup>a</sup>	7
Chen Yan	2019	retrospective	2016/1-2017/12	The First Affiliated Hospital of Zhejiang University	165/96	121/69	61/63 <sup>b</sup>	8
Chen Jinyin	2018	retrospective	2014/3-2016/2	Zhuji People's Hospital	63/23	39/19	65.0 +/- 13.0/65.9-13.2 <sup>a</sup>	7
Ma Liping	2016	retrospective	2009/1-2014/12	The Second Affiliated Hospital of Nanjing Medical University	76/15	51/9	39/9 <sup>c</sup>	7
Kang to fly	2019	retrospective	2011/1-2016/12	Ningxia Medical University General Hospital	125/32	66/22	53/64.5 <sup>b</sup>	8
Dong Jin wave	2019	retrospective	2015/2-2018/2	Yantai Laiyang Central Hospital	289/61	132/30	160/46 <sup>c</sup>	8

Note: A: mean ± standard deviation B: median C: Number of cases (age > 60 years).

### 3.3. Meta-analysis of Death Factors of KP Bloodstream Infection

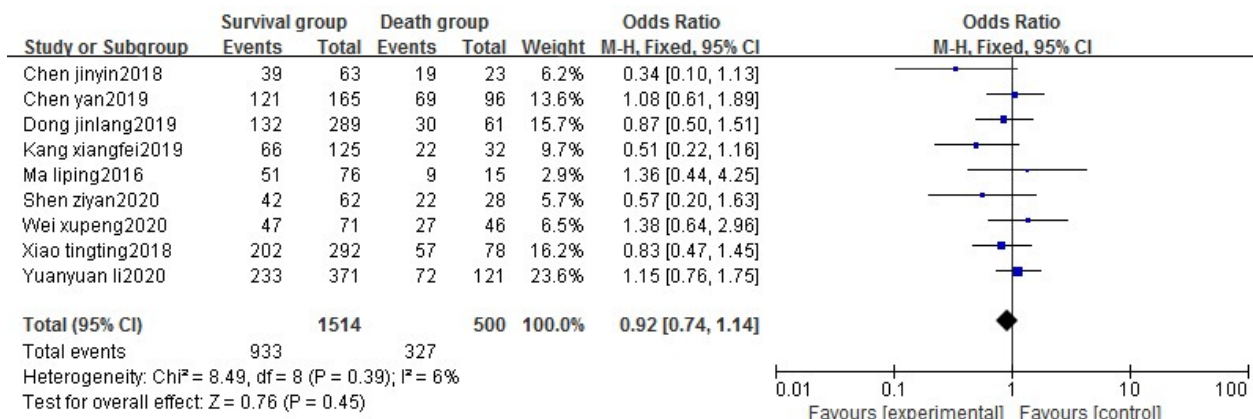
#### 3.3.1. Heterogeneity Analysis

The heterogeneity of the literature of included in the analysis, the results showed that age, male, history of hospitalization, history of ICU stay, diabetes, hypertension, cerebrovascular disease, heart disease, kidney disease, lung disease, liver disease, liver abscess, blood system tumor, hypoalbuminemia, operation history, history of hemodialysis, deep venipuncture, indwelling gastric tube, parenteral nutrition, use radiotherapy/chemotherapy, hormone and immune inhibitor use, antibiotics (beta lactam, quinolone, for ring element, cephalosporins) the use of the literature does not exist between groups of heterogeneity ( $I^2 < 50\%$ ,  $P > 0.05$ ), so a fixed-effect model was used for meta-analysis. There was heterogeneity among groups in the use of mechanical ventilation, indwelling catheter and carbapenems ( $I^2 > 50\%$ ,  $P < 0.05$ ), so the random effect model was used for meta-analysis. Meta analysis results show that the history of hospitalization, history of ICU stay, high blood pressure, heart disease, kidney disease, lung disease, liver abscess, hypoalbuminemia, hemodialysis, mechanical ventilation, deep venipuncture, indwelling gastric tube, parenteral nutrition, placing a urinary catheter use radiotherapy/chemotherapy, hormone and immune inhibitor use, antibiotics (beta lactam, carbon black, alkene, quinolone, for ring element, cephalosporins) use is a major risk factor for killing KP bloodstream infections, specific see table 2 and figure 2.

**Table 2.** Meta-analysis results of risk factors for death from KP bloodstream infection

Risk factors	Merge the number	Survival/death group		OR/MD[95%CI]	Z	P	Heterogeneity of study design			Research model	Egger's Test (P)
		Events	Total				$\chi^2$	P	$I^2$ (%)		
Age	3	58.56 + / - 16.35	59.89 + / - 14.72	1.96 [4.80, 0.88]	1.35	0.18	3.17	0.20	37.0	fixed	0.667
Men	9	327/932	500/1514	0.91 [0.74, 1.14]	0.81	0.42	8.20	0.41	2.0	fixed	0.137
In the history of hospital	4	171/430	237/802	0.45 [0.33, 0.63]	4.80	< 0.00001	0.40	0.94	0.0	fixed	0.812
The history of ICU stay	6	224/177	1029/361	0.26 [0.20, 0.34]	9.83	< 0.00001	5.74	0.33	13.0	fixed	0.014
Basic diseases											
diabetes	5	212/76	746/301	1.09 [0.80, 1.49]	0.55	0.58	2.29	0.68	0.0	fixed	0.884
hypertension	4	237/83	799/220	0.69 [0.50, 0.95]	2.29	0.02	2.76	0.43	0.0	fixed	0.012
heart disease	4	104/55	794/251	0.60 [0.42, 0.88]	2.64	0.008	4.87	0.18	38.0	fixed	0.346
cerebrovascular disease	3	31/9	210/84	1.16 [0.51, 2.62]	0.36	0.72	0.99	0.61	0.0	fixed	0.129
kidney disease	5	60/42	746/301	0.52 [0.34, 0.79]	3.06	0.002	6.72	0.15	41.0	fixed	0.928
lung disease	6	164/74	1161/349	0.53 [0.38, 0.75]	3.62	0.0003	9.76	0.08	49.0	fixed	0.177
liver disease	3	130/37	520/197	1.38 [0.91, 2.09]	1.51	0.13	1.64	0.44	0.0	fixed	0.244

liver abscess	3	67/3	417/129	6.97 [2.32, 20.91]	3.46	0.0005	0.03	0.98	0.0	fixed	0.502
hematologic tumor	3	92/46	607/263	0.84 [0.57, 1.26]	0.83	0.41	0.19	0.91	0.0	fixed	0.621
hypoproteinemia	3	158/58	430/121	0.56 [0.36, 0.85]	2.69	0.007	3.04	0.22	34.0	fixed	0.599
Invasive operation											
surgery	8	380/147	1225/439	0.87 [0.69, 1.10]	1.16	0.25	3.42	0.84	0.0	fixed	0.142
hemodialysis	6	85/65	1029/361	0.41 [0.29, 0.58]	4.96	< 0.0001	3.52	0.62	0.0	fixed	0.100
mechanical ventilation	8	263/153	1143/379	0.39 [0.22, 0.67]	3.36	0.0008	25.4	0.00	72.0	random	0.948
deep vein catheters	5	191/145	721/244	0.25 [0.18, 0.34]	8.69	< 0.0001	5.05	0.28	21.0	fixed	0.172
gastric intubation	3	162/976	558/181	0.33 [0.23, 0.47]	6.10	< 0.0001	2.50	0.29	20.0	fixed	0.890
a urinary tube	6	419/199	1210/366	0.48 [0.28, 0.83]	2.63	0.008	21.2	0.00	76.0	random	0.528
parenteral nutrition	4	215/106	847/242	0.44 [0.32, 0.59]	5.42	< 0.0001	5.85	0.12	49.0	fixed	0.304
Radiotherapy/chemot	3	124/72	607/263	0.70 [0.50, 0.99]	2.00	0.05	0.98	0.61	0.0	fixed	0.729
Hormone use	5	154/86	1024/373	0.51 [0.38, 0.69]	4.31	< 0.0001	3.26	0.52	0.0	fixed	0.632
Immunosuppressive use	5	127/69	961/369	0.59 [0.42, 0.82]	3.16	0.002	4.50	0.34	11.0	fixed	0.812
Antibiotic use											
β-lactam	4	283/139	1023/306	0.47 [0.36, 0.62]	5.31	< 0.0001	3.16	0.37	5.0	fixed	0.039
carbapenems	4	250/151	1023/306	0.35 [0.21, 0.57]	8.23	< 0.0001	9.25	0.03	68.0	random	0.200
quinolone class	4	198/78	1023/306	0.73 [0.53, 1.00]	1.98	0.05	2.99	0.39	0.0	fixed	0.020
tigecycline	4	87/64	1023/306	0.36 [0.25, 0.52]	5.50	< 0.0001	5.47	0.14	45.0	fixed	0.247
cephalosporin	3	126/50	652/185	0.46 [0.30, 0.71]	3.51	0.004	1.88	0.39	0.0	fixed	0.195



**Figure 2.** Forest plot of the relationship between male and risk factors of death from KP bloodstream infection

**3.3.2. Sensitivity Analysis**

For the risk factors with heterogeneity among the included studies, fixed effect and random effect models were used to calculate the combined OR value and 95%CI of each risk factor of KP bloodstream infection death. Among the factors analyzed by fixed effect model, the results of male, diabetes, cerebrovascular disease, liver disease, hematological tumor and surgical history included invalid value 1. The use of mechanical ventilation, indignant catheter and carbapenems was analyzed using a random-effect model, which did not include invalid value 1. There was no significant difference in the combined results of other risk factors under the two models, and the combined results were basically stable, as shown in Table 3.

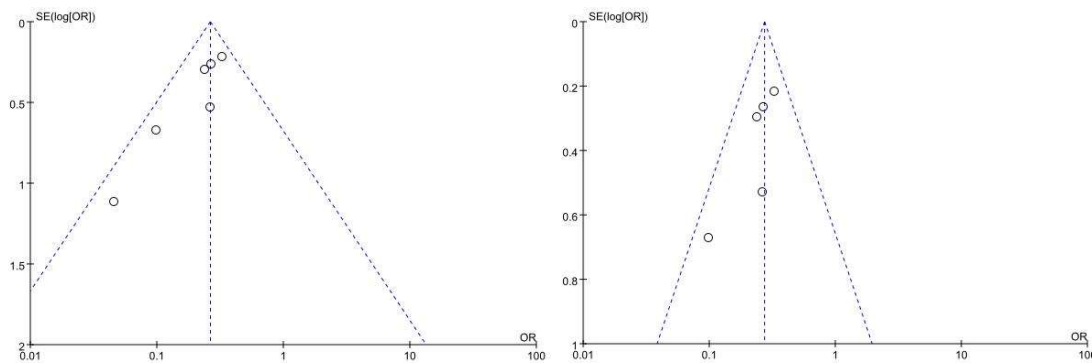
**Table 3.** Analysis of the sensitivity of the two models to risk factors of death due to KP bloodstream infection

Risk factors for	Fixed effect model OR/MD[95%CI]	Random effects model OR/MD[95%CI]
Mechanical ventilation	0.39 [0.30, 0.50]	0.39 [0.22, 0.67]
A urinary tube	0.44 [0.35, 0.56]	0.48 [0.28, 0.83]
Carbapenems are used	0.32 [0.25, 0.42]	0.35 [0.21, 0.57]

**3.3.3. Publication Bias**

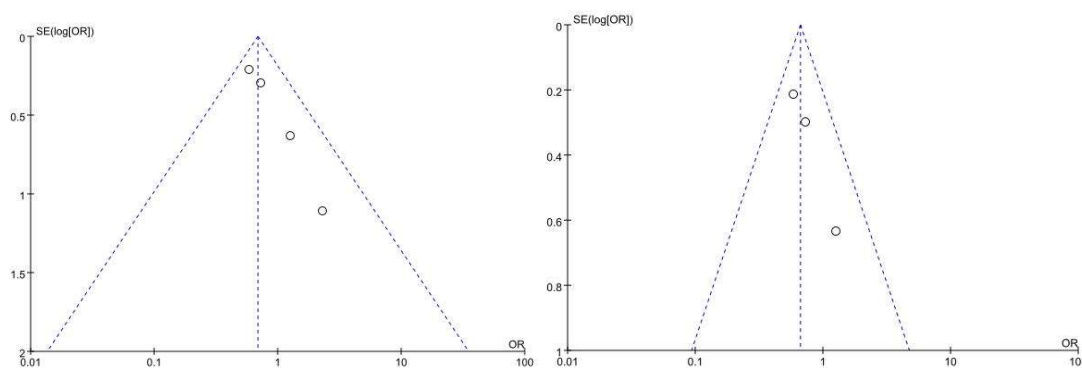
Egger linear regression is used to include literature publication bias analysis of risk factors, which plays a significant role in the history of ICU stay bias (Egger value (P < 0.5), the funnel, according to the figure Chen Jinyin center for research and funnel figure axis deviation from far away, reference Chen Jinyin research data showed that its weight accounts for only 4.3% of the research, hence the "removal of one-way method" to remove Chen Jinyin after the research on the data back to Meta analysis, publication bias results show Egger value P > 0.05 (0.089), funnel figure not seen obvious asymmetry (figure 3), prompt the results there is no bias, And P < 0.05, the difference was statistically significant, so it was accepted.

Plays a significant role in hypertension bias (Egger value P < 0.5), the funnel, according to the figure Chen Jinyin center for research and funnel figure axis deviation from far away, reference Chen Jinyin research data shows that the weight accounts for only 1.5% of the research, hence the "removal of one-way method" to remove Chen Jinyin Meta analysis was carried out on the data again after research, publication bias results show Egger value P > 0.05 (0.085), funnel figure not seen obvious asymmetry (figure 4), prompt the results there is no bias, and P values < 0.05, the difference was statistically significant, to accept it.



**Figure 3.** a to b

Note: a: The 95%CI publication bias funnel of ICU stay history before one-way study was removed; b: The 95%CI of ICU stay history was published skewed funnel plot after the one-way study was removed.



**Figure 4.** c to d

Note: c: The publication bias funnel plot of 95%CI of hypertension before one-way study was removed; d: The 95%CI publication bias funnel plot of hypertension before one-way study was removed

### 4. Discuss

A total of 9 studies were included in this paper, mainly distributed in China, and the results reflected the main factors leading to death of PATIENTS with KP BSI in China's medical environment. The NOS score indicated that all the 9 studies included in this study were of high quality. The included study data were complete and the control conditions were similar, which greatly reduced the possible experimental errors caused by data combination between studies caused by the interference of unrelated factors. Therefore, the analysis results of this study were highly reliable.

Existed in this paper, the results showed that the sufferer of basic diseases such as hypertension, heart disease, kidney disease, lung disease, liver abscess, malignant tumor, hypoalbuminemia is a risk factor for death in patients with KP BSI, publication bias results suggest hypertension biased, through the "removal of single method" to remove the weight after a small study, to bias the data analysis, the result shows that there is no obvious bias, funnel chart its asymmetry declined significantly earlier (figure 3), analysis of data after removal of individual research results from the previous did not see obvious changes, to accept; However, there are few literatures on the analysis of hypertension factors, and the funnel plot analysis is not very convincing. Therefore, the funnel plot is only used as a reference for this analysis, and the interpretation of the results is mainly based on data analysis. Finally, hypertension, heart disease, kidney disease, lung disease, liver abscess, hypoproteinemia and other related basic

diseases were considered as risk factors leading to DEATH of KP bloodstream infection, which was consistent with previous relevant research results[18-20].

Hospitalization history and ICU stay history are risk factors leading to death of KP bloodstream infection, which may be due to frequent hospitalization history and ICU stay history greatly increasing patients' exposure to various pathogenic bacteria. In addition, this is also related to the clinical characteristics of ICU patients themselves, ICU patients tend to be in critical condition, low immunity, complex underlying diseases and other characteristics[21-24]Therefore, ICU patients are exposed to more risk factors and have a higher mortality rate due to pathogens than other patients. Studies have shown that the mortality rate of bloodstream infection in patients with ICU admission history is several times higher than that in other departments[25].

Invasive procedures such as hemodialysis, mechanical ventilation, deep vein catheterization, indwelling gastric tube, indwelling urinary tube, and parenteral nutrition are risk factors for increasing the mortality of KP bloodstream infection. Invasive procedures can disrupt the body's normal barriers and provide the damaged parts of the body with the opportunity to contact external risk factors, which greatly increases the risk of infection in patients with already low immunity[26].

The use of antibiotics ( $\beta$ -lactam, carbapenems, quinolones, tigecycline, cephalosporins) is a risk factor for death from KP bloodstream infection. In recent years, the drug resistance of *Klebsiella pneumoniae* has become increasingly serious[27-29], because unreasonable drug use or experiential drug use will increase the drug resistance rate of bacteria, narrowing the range of available drugs in clinical practice. If attention is not paid in time and appropriate control measures are not taken, it will eventually lead to the situation of no drugs available in clinical practice. Therefore, the rational use of antibiotics in clinical work is particularly important. In this regard, clinicians should strengthen communication with auxiliary departments in their daily work, and make the most correct drug selection based on experimental drug sensitivity results, so as to reduce the high fatality rate of KP BSI patients caused by unreasonable use of antibiotics.

Other factors such as radiotherapy/chemotherapy, hormone use, and immunosuppressive use were associated with higher mortality from KP bloodstream infection, which was consistent with the results of all studies included in this study.

At present, age, diabetes, malignant tumor, surgical history and other factors have not been found to be associated with the high mortality of KP bloodstream infection, which is related to Liu's study[30]The results were consistent. In addition, this study found that gender is not a high case fatality rate factor, KP BSI patients that do not agree with liu's research results, but with this article are included in the study results are consistent, this may be due to liu into the research mainly foreign literature, and in research of this article is mainly caused by the domestic literature, the choice of different into literature, its corresponding regional distribution of different patients, patients with physical differences in the results may not be consistent.

To sum up, history of hospitalization, history of ICU stay, high blood pressure, heart disease, kidney disease, lung disease, liver abscess, hypoalbuminemia, hemodialysis, mechanical ventilation, deep venipuncture, indwelling gastric tube, parenteral nutrition, placing a urinary catheter use radiotherapy/chemotherapy, hormone and immune inhibitor use, antibiotics (beta lactam, carbon green alkene, quinolone, for ring element, cephalosporins) is the main risk factors of KP BSI patients died. Clinical medical staff should strengthen prevention and control of common risk factors leading to death of KP BSI patients, actively treat related underlying diseases, strengthen communication with auxiliary departments, and minimize the death rate of KP BSI patients.

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