

Meta-analysis of Risk Factors for Mortality in Patients with *Acinetobacter Baumannii* Bloodstream Infection

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Abstract: Background: Patients with *Acinetobacter baumannii* bloodstream infection (ABBI) have a poor prognosis and high mortality. Early identification of risk factors for death in patients with ABBI, and appropriate prevention and control measures are extremely important to reduce the mortality. Objective: To systematically evaluate the risk factors of ABBI, which provide evidence for reducing the incidence and mortality of patients. Methods: The published articles and reference works on prognosis risk factors in patients with ABBI were retrieved from inception to January 2021 in the following databases: PubMed, Web of Science, Embase, CNKI, Wanfang and VIP. Those studies that met the inclusion criteria were performed quality evaluation and data analysis. Meta-analysis was performed by the statistical software Stata13.0. Results: A total of 24 articles were included, including 1 203 patients in the death group and 1 319 patients in the survival group. Among the 24 included study factors, 15 showed statistically significant differences ($P < 0.01$), including: age (MD=0.19, 95%CI: 0.08~0.30, $P < 0.01$), APACHE II (MD=0.48, 95%CI: 0.06~0.91, $P = 0.03$), ICU admission (OR=1.91, 95%CI: 1.12~3.26, $P = 0.02$), shock (OR=4.28, 95% CI: 1.05~17.49, $P = 0.04$), septic shock (OR=8.36, 95%CI: 3.71~18.82, $P < 0.01$), renal damage (OR=1.57, 95%CI: 1.19~2.07, $P < 0.01$), diabetes (OR=1.31, 95%CI: 1.03~1.68, $P = 0.03$), malignant tumor (OR=1.56, 95%CI: 1.02~2.37, $P = 0.04$), liver disease (OR=1.93, 95%CI: 1.25~3.00, $P < 0.01$), hormonal used (OR=5.46, 95%CI: 3.12~9.56, $P < 0.01$), immunosuppression (OR=2.73, 95%CI: 1.82~4.1, $P < 0.01$), mechanical ventilation (OR=3.17, 95%CI: 2.34~4.29, $P < 0.01$), deep vein catheterization (OR=2.02, 95%CI: 1.56~2.61, $P < 0.01$), indwelling urinary catheter (OR =2.53, 95%CI: 1.66~3.84, $P < 0.01$), indwelling gastric tube (OR=1.79, 95%CI: 1.21~2.65, $P < 0.01$). Conclusion: The severity of the patient's underlying disease, using of hormones and immunosuppressants, and various invasive operations were the main risk factors for high mortality in ABBI patients. It was necessary to focus on older patients, dynamically monitor the APACHE II score, carefully evaluate the effect of hormone and immunosuppressant application, and strictly control the indications of invasive operation or treatment.

Keywords: *Acinetobacter Baumannii*, Bloodstream Infection, Risk Factors, Mortality, Meta-analysis

1. Introduction

Acinetobacter baumannii (AB) is a kind of gram-negative bacilli, which has strong acquired drug resistance and transmission ability [1]. It has become one of the important pathogenies of global hospital infection with the incidence rate increasing. In recent years, the incidence of bloodstream infections caused by AB has been on the rise [2]. About 2% ~ 5% of hospital acquired bloodstream infections are caused by AB [3]. AB bacteremia can significantly prolong the length of hospital stay and increase the cost of treatment. The prognosis

of patients is poor and the mortality rate is high. Septicemia or bacteremia caused by AB is a common cause of death in patients, with a mortality rate of 27%~35% [3, 4]. In the intensive care unit (ICU), the mortality rate of *Acinetobacter baumannii* bloodstream infection (ABBI) patients reaches 35%~50% [4]. Therefore, early identification of risk factors for death in patients with ABBI, and targeted application of prevention and control measures are extremely important for reducing the mortality of patients. A number of studies [5-10] have been carried out on the risk factors for the death of ABBI patients. However, the risk factors obtained from different

studies are not the same, and the results are also different. While this study used meta-analysis to conduct the qualitative and quantitative comprehensive analysis of related articles, and systematically evaluate the risk factors of death in ABBI patients. In order to provide an evidence-based basis for guiding the clinical adjustment of treatment and nursing programs and improving the prognosis of patients.

2. Materials and Methods

2.1. Information Retrieval

The published studies and reference works on mortality risk factors in patients with ABBI were retrieved from inception to January 2021 in the following databases: PubMed, Web of Science, Embase, CNKI, Wanfang and VIP. The main search terms were [Title/Abstract]: ('Acinetobacter baumannii' OR 'A baumannii' OR 'Acinetobacter') AND ('bacteremia' OR 'bloodstream infection' OR 'blood infection' OR 'septicemia' OR 'sepsis') AND ('mortality' OR 'fatality' OR 'lethality' OR 'prognosis' OR 'predictor' OR 'survival') AND ('risk factors' OR 'influencing factors'). The corresponding Chinese search terms were used for the Chinese databases. In addition, the references identified by this strategy were searched to select relevant articles. Grey article or unpublished data were not searched for this study.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria

Studies reporting risk factors of mortality in patients infected with ABBI were included. The cases met the diagnostic criteria of bloodstream infection, and the blood culture suggested *Acinetobacter baumannii* infection. The mean difference (MD) or odds ratio (OR) value and 95% confidence intervals (CI) of multivariate analysis or the data that can calculate OR value and 95% CI were included in the articles.

2.2.2. Exclusion Criteria

Repetitive published article, reviews, systematic reviews, meta-analyses, guidelines, editorials, case reports, animal research, in vitro studies, and research that focused on specific population (such as children or newborns). Studies with research design defects, no controlled studies, article with incomplete statistical data, unable to obtain or value and 95% CI of risk factors, were also excluded.

2.3. Evaluation of Study Quality

Endnote X9 was used for articles management and duplicate checking. Two authors (Xu H. and Haiyan H.) independently screened and reviewed each study manually for eligibility. According to the Newcastle Ottawa scale (NOS) score, the articles meeting the above criteria were assessed with 0-9 for quality assurance. Studies with a $NOS \geq 6$ were included in this analysis. Any disagreement was resolved by the adjudicating senior authors (Weitao L. and Wanxian L.).

2.4. Data Extraction and Statistical Methods

Excel 2016 was used to design a unified document information extraction table, including: study author, publication year, country, design, number of grouped cases, research risk factors, and NOS score. Two authors (Xu H. and Haiyan H.) independently extracted relevant information of the included articles according to the unified table, and then cross-checked. Stata 13.0 were used for statistical analysis. The measurement data used MD and 95% CI, the count data used OR and 95% CI, and the inspection level was $\alpha = 0.05$. The heterogeneity test was analyzed using the chi-square test. When ($P > 0.10$, $I^2 < 50\%$), the heterogeneity was small, which the fixed effects model (FE) was used. When ($P \leq 0.10$, $I^2 \geq 50\%$), the random effects model (RE) was used, and briefly analyzed the causes of heterogeneity. Egger's method was used to analyze the publication bias quantitatively.

3. Results

3.1. The Articles Search Results

A total of 678 articles were retrieved in this study, including: PubMed (n=193), Web of Science (n=162), Embase (n=79), CNKI (n=143), Wanfang (n=71), VIP (n=30). After duplicate checking with Endnote X9, 509 articles were remained, and 438 articles were excluded by reading the title and abstract. About 47 studies were excluded by reading the full text, while 24 studies were finally included. Flow diagram of studies identified, excluded, and included were shown in Figure 1.

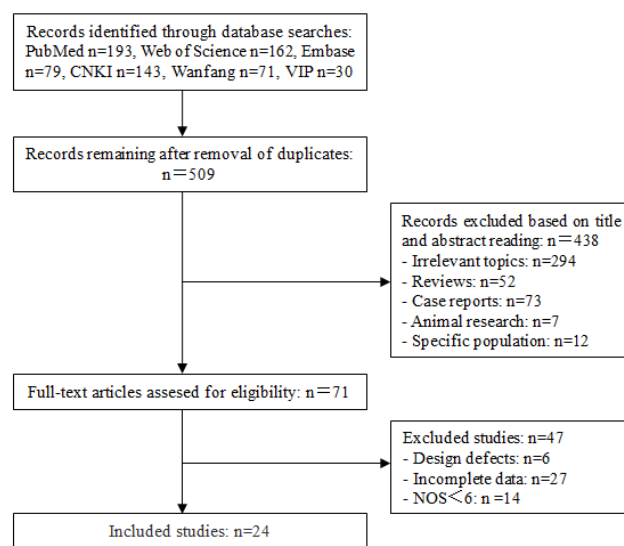


Figure 1. Flow diagram of studies identified, excluded, and included

3.2. Basic Characteristics of the Included Studies

The 24 included articles were retrospective or case-control studies. After scoring by NOS standards, there were 10 articles with 8 points, 11 articles with 7 points, and 3 articles with 6 points. The overall quality of those studies was good, which 12 papers published in the last five years. However, the sample size of the included article was small, most studies had

only dozens cases, as shown in *Table 1*. A total of 2 522 1 319 were in the survival group. patients with ABBI, which 1 203 were in the death group and

Table 1. The baseline information of the included studies.

Study Author	Year	Country	Design	Death	Survival	Risk factors	NOS
Yu K. et al. [5]	2021	China	R/MC	33	75	ABCFHIOPQRS	8
Gu Y. et al. [6]	2021	China	Case-control/ SC	21	26	ACDJKLRSTW	8
Zhou H. et al. [7]	2019	China	R/MC	154	120	ABCDEFSTUVW	8
Papadimitriou-O. M. et al. [8]	2017	Greece	Case-control/ SC	51	78	ABCFHIJKLMPSTU	8
Ballouz T. et al. [9]	2017	Lebanon	R/SC	58	32	ABEFGHIJKLMPTUVWX	8
Wang, X. et al. [10]	2017	China	R/MC	13	27	ABCDEFKMPQ	6
Yanyan Z. et al. [11]	2017	China	R/SC	40	38	ABCDFHILMTU	7
Zhang Y. et al. [12]	2017	China	R/SC	53	95	ABDFGHILMOPUV	7
Gu Z. et al. [13]	2016	China	R/SC	49	73	ADGHIJKLMNQTVWX	7
Lee YT. et al. [14]	2016	China	R/MC	45	72	ADEV	7
Liu CP. et al. [15]	2016	China	R/SC	106	76	ADFHIJKLMTVW	7
Guo N. et al. [16]	2016	China	R/SC	39	48	ACDFOPQRSTV	7
Freire MP. et al. [17]	2015	Brazil	R/SC	77	15	AFJOS	7
Long Y. et al. [18]	2015	China	R/SC	35	17	ABCEGIKLORST	6
Liu, Q. et al. [4]	2015	China	R/SC	53	129	ABDFJKLMOPSTX	8
Nutman A. et al. [19]	2014	Israel	Case-control / SC	83	89	ADQV	6
Park SY. et al. [20]	2013	Korea	R/SC	42	81	ABDEOPQRSTUVX	8
Kim SY. et al. [21]	2012	Korea	Case-control/ SC	79	20	ABCDHIJKLTUWX	7
Esterly JS. et al. [22]	2011	United States	R/SC	31	48	ABOQV	8
Song JY. et al. [23]	2011	Korea	R/SC	15	13	ABGHJKLMNOQTX	8
Anunnatsiri S. et al. [24]	2011	Thailand	R/SC	34	15	ABDFGHIJKUV	7
Routsi C. et al. [25]	2010	Greece	R/MC	44	52	ABDEOPQTUX	7
Tseng YC. et al. [26]	2007	Taiwan, China	R/SC	27	29	FGHJKLNQSUVWX	8
Choi JY. et al. [27]	2005	Korea	R/SC	21	51	ABFOPQRS	7

R, retrospective; SC, single center; MC, multicenter. Among the risk factors: A: sex, B: age, C: APACHE II, D: ICU admission, E: shock, F: septic shock, G: cerebrovascular disease, H: cardiovascular disease, I: hypertension, J: renal damage, K: diabetes, L: malignant tumor, M: lung disease, N: liver disease, O: mixed infection, P: hormonal used, Q: immunosuppression, R: carbapenem antibiotic, S: combined antibiotic, T: mechanical ventilation, U:tracheal intubation/incision, V: deep vein catheterization, W: indwelling urinary catheter, X: indwelling gastric tube.

3.3. Results of Meta-analysis

Among the 24 included study factors, 15 showed statistically significant differences ($P<0.01$). These risk factors included: age, APACHE II, ICU admission, shock, septic shock, renal damage, diabetes, malignant tumor, liver disease, hormonal used, immunosuppression, mechanical ventilation, deep vein catheterization, indwelling urinary catheter, indwelling gastric tube, as shown in *Table 2*. In the analysis of publication bias, the probability of publication deviation among all factors included in the study were small (Egger's test $P\geq 0.05$, *Table 2*). Taken the risk factors of septic shock, mechanical ventilation, deep vein catheterization, indwelling urinary catheter as examples to draw forest plots, as shown in *Figure 2-5*.

Table 2. Heterogeneity test and meta-analysis of risk factors for mortality in patients with ABBI at included.

Type of factor	No. of studies	No. of patients in studies reporting specific data		Heterogeneity Test		Analytical Model	Pooled OR/MD	95%CI	P value	Egger's test	
		Death/ Total	Survival/ Total	P value	I ² (%)					t	P> t
Sex (male/ total)	23	769/1 227 ^s	709/1 213 ^s	0.58	0	FE	0.89	0.75~1.06	0.18	0.357	0.492
Age	17	N/A	N/A	0.1	32	RE	0.19*	0.08~0.30	0.00	-0.396	0.600
APACHE II	9	N/A	N/A	<0.01	75.2	RE	0.48*	0.06~0.91	0.03	3.290	0.274
ICU admission	10	386/686	414/563	0.00	72	RE	1.91	1.12~3.26	0.02	0.912	0.617
Shock	5	32/114	132/196	<0.01	77.4	RE	4.28	1.05~17.49	0.04	3.392	0.615
Septic shock	12	167/697	482/769	<0.01	86.6	RE	8.36	3.71~18.82	0.00	2.198	0.274
Cerebrovascular disease	10	78/303	58/266	1.69	30	FE	0.99	0.63~1.55	0.96	0.384	0.892
Cardiovascular disease	13	217/776	158/747	0.98	0	FE	0.83	0.63~1.09	0.18	-0.528	0.154
Hypertension	6	121/395	73/260	0.07	50	FE	1.01	0.69~1.48	0.97	-3.545	0.459
Renal damage	16	111/847	195/935	0.50	0	FE	1.57	1.19~2.07	0.00	0.603	0.242
Diabetes	16	158/849	230/893	0.18	23.8	FE	1.31	1.03~1.68	0.03	0.588	0.506
Malignant tumor	15	158/810	210/788	<0.01	56.7	RE	1.56	1.02~2.37	0.04	-1.605	0.186
Lung disease	17	136/866	150/905	0.23	19.2	FE	0.98	0.75~1.29	0.91	-0.599	0.424
Liver disease	9	46/571	64/506	0.27	19	FE	1.93	1.25~3.00	0.00	0.757	0.449
Mixed infection	14	299/749	295/673	0.65	0	FE	1.16	0.92~1.47	0.20	-0.301	0.568
Hormonal used	5	54/179	106/205	0.63	0	FE	5.46	3.12~9.56	0.00	-1.99	0.219
Immunosuppression	7	51/308	99/316	0.27	20.6	FE	2.73	1.82~4.10	0.00	-0.632	0.684
Carbapenem antibiotic	5	49/153	43/94	<0.01	73.2	RE	1.56	0.50~4.84	0.44	-2.698	0.726

Type of factor	No. of studies	No. of patients in studies reporting specific data		Heterogeneity Test		Analytical Model	Pooled OR/MD	95%CI	P value	Egger's test	
		Death/ Total	Survival/ Total	P value	I ² (%)					t	P> t
Combined antibiotic	9	206/409	220/451	0.02	67.9	RE	1.41	0.74~2.70	0.30	-0.214	0.881
Mechanical ventilation	12	362/622	452/574	0.17	28.4	FE	3.17	2.34~4.29	0.00	-0.591	0.758
Tracheal intubation/incision	9	208/552	179/396	<0.01	63.9	RE	1.68	0.73~3.83	0.22	2.236	0.051
Deep vein catheterization	12	424/710	447/588	0.37	7.3	FE	2.02	1.56~2.61	0.00	1.351	0.165
Indwelling urinary catheter	7	215/311	294/338	0.76	0	FE	2.53	1.66~3.84	0.00	1.371	0.130
Indwelling gastric tube	7	131/248	157/247	0.91	0	FE	1.79	1.21~2.65	0.00	0.506	0.489

APACHE II: Acute Physiology and Chronic Health Evaluation II score; N/A: not applicable; OR: odds ratio; MD: mean difference; §sex: male/total; * Pooled MD

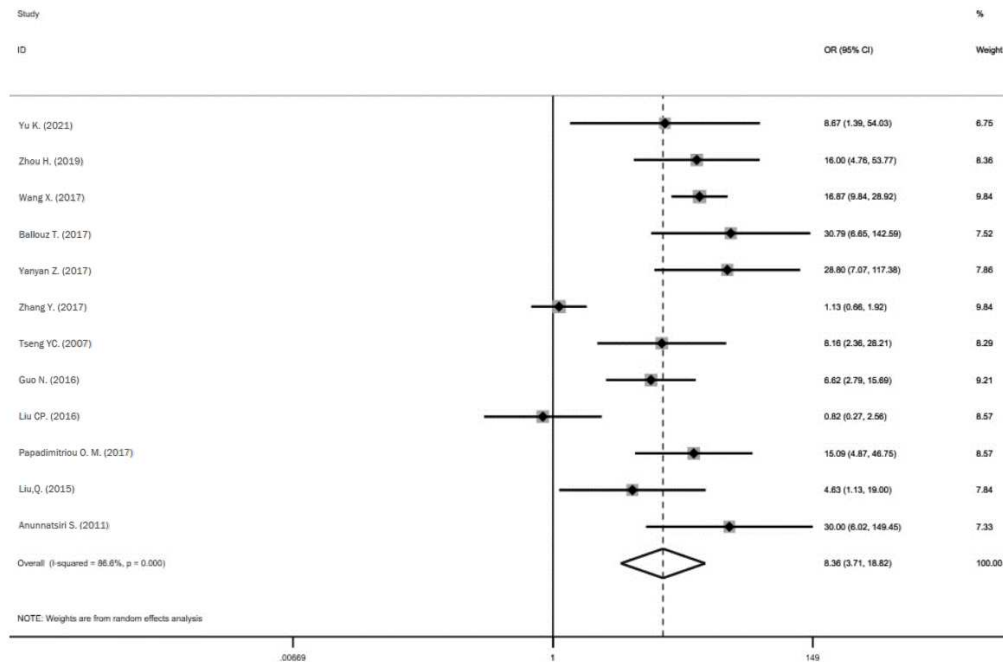


Figure 2. Forest plot and meta-analysis of septic shock.

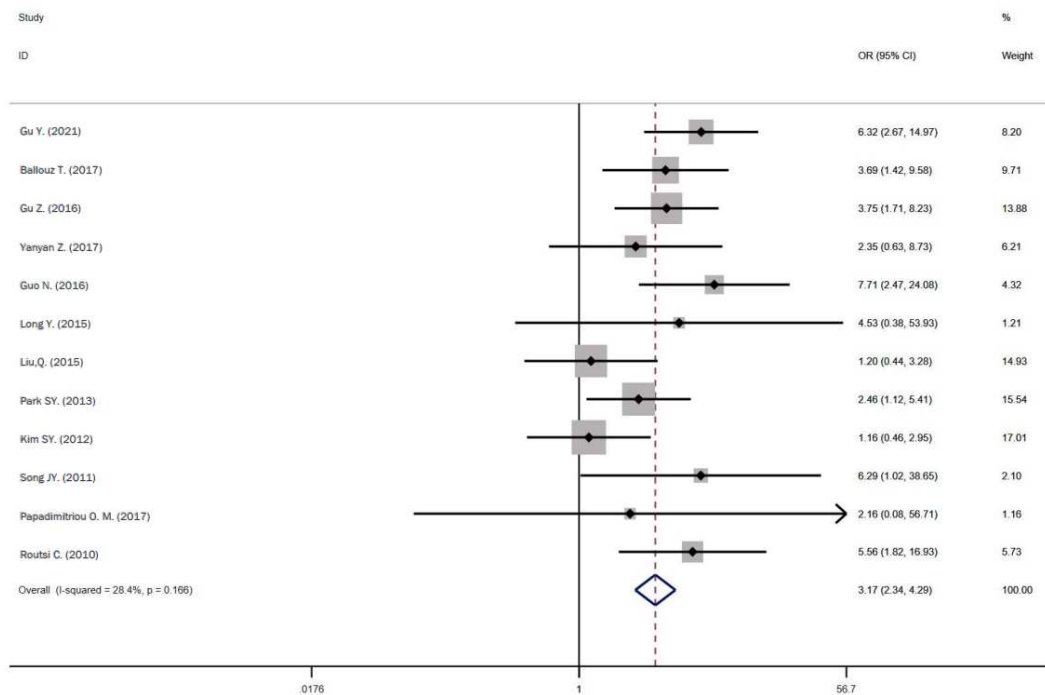


Figure 3. Forest plot and meta-analysis of mechanical ventilation.

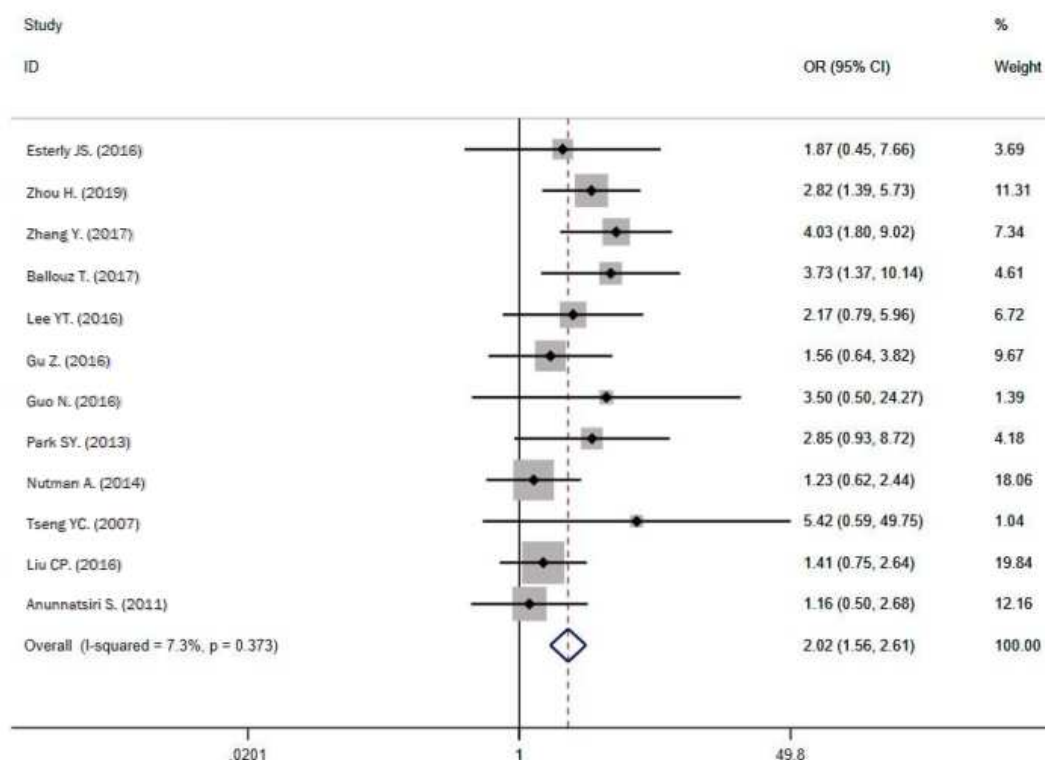


Figure 4. Forest plot and meta-analysis of deep vein catheterization.

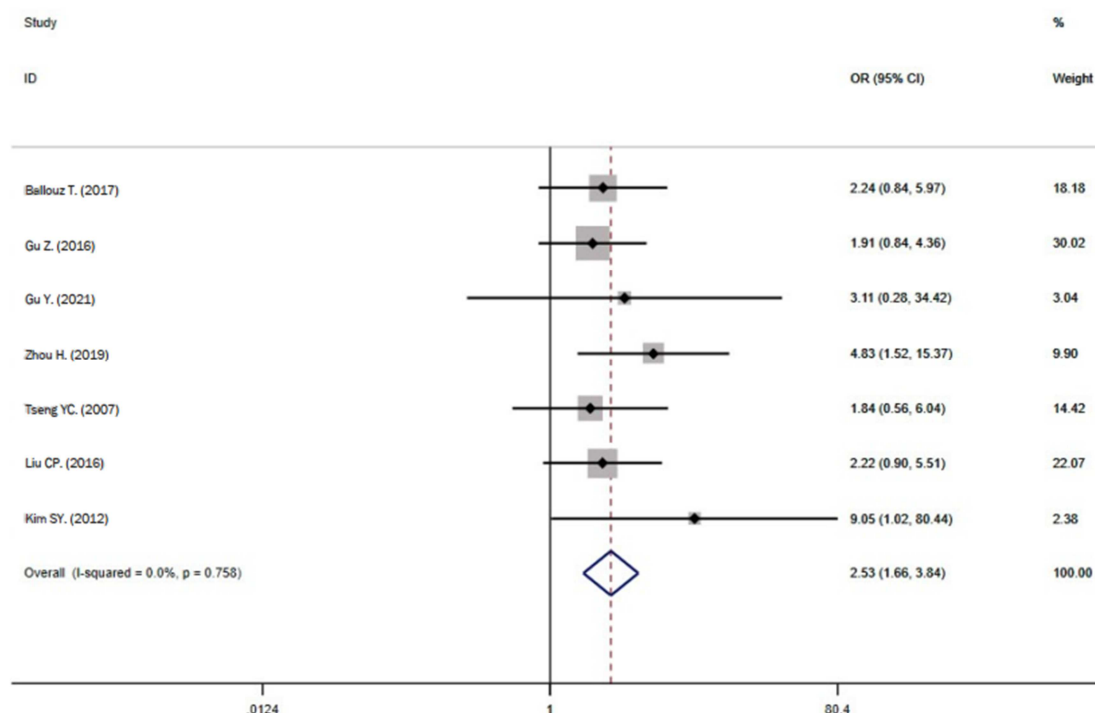


Figure 5. Forest plot and meta-analysis of indwelling urinary catheter.

4. Discussion

AB is one of the main pathogenic bacteria causing nosocomial infections. Because of its strong transmission ability and high drug resistance rate [28], it is widely prevalent

in global medical institutions. In recent years, the incidence of bloodstream infections caused by AB has been on the rise [6]. The prognosis of patients is poor and the mortality rate is high. Early identification of the risk factors for the death of ABBI patients and the targeted adoption of reasonable preventive measures are extremely important for reducing the mortality

of patients. In this paper, meta-analysis was used to conduct a qualitative and quantitative comprehensive analysis of 24 related articles, and systematically evaluate the risk factors of death in ABBI patients.

The results of this study shown that age, APACHE II, ICU admission, shock, septic shock, renal damage, diabetes, malignant tumor, liver disease, hormonal used, immunosuppression, mechanical ventilation, deep vein catheterization, indwelling urinary catheter, indwelling gastric tube were important risk factors for the death of ABBI patients. The elderly patients might have serious underlying diseases. The patients had poor nutritional status and weakened immune function, leading to poor clinical prognosis. The APACHE II score was a quantitative index for clinical evaluation of the severity of the condition of critically ill patients and the prognosis of the disease. It was currently the most authoritative evaluation system for the condition. The study by Knaus WA et al. [29] showed that after evaluating 5 815 critically ill patients, they found that the APACHE II score was directly related to the actual mortality of the patient. The higher of the APACHE II score, the patient's condition was more serious, and the prognosis was worse. The patients admitted to ICU were in critical condition, and they would use a lot of antibiotics and invasive operations during the treatment process. Compared with the patients in the general wards, AB infection had more chances and higher mortality rate [30]. In addition, Xiao D. et al. [31] research suggested that septic shock in the ICU would affect the prognosis of patients infected with AB, which was consistent with the results of this study.

The results of this study showed that the use of hormones and immunosuppressants were risk factors for poor prognosis of ABBI. Clinical use of large doses of hormones and immunosuppressants to suppress abnormal immunity, but also inhibit the body's normal humoral immunity and cellular immunity, resulting in reduced immune function of patients, easily to induce infection. It was suggested that the clinical significance of hormone and immunosuppressant should be evaluated carefully. At the same time, invasive mechanical ventilation, deep vein catheterization, indwelling urinary catheter, indwelling gastric tube were the high risk factor for death in patients with ABBI. It has been confirmed in study [32] that mechanical ventilation was a high risk factor for death in patients with ABBI. The probability of microbial colonization would be significantly increased when the patient's airway was open. Similarly, deep vein catheterization, indwelling catheter and indwelling gastric tube all form artificial cavities in patients, which were also exposed to ward environment in the process of treatment and nursing. That could easily lead to the occurrence and development of ABBI, and eventually lead to poor clinical prognosis of patients. Therefore, clinicians should strictly control the indications of invasive procedures and minimize unnecessary catheterization.

There are some limitations in this study: Because the research objects of the included articles came from many countries and regions, there had different levels of infection

control and measures, which made some research factors have some heterogeneity. In some studies, the pooled effect size was not calculated due to the inconsistency in the definition of the research factors. Some of the studies had non-standard control selection, comparability between groups, and the determination of exposure factors were not clearly described, which suggested that the original design of these studies needed to be further standardized. Sensitivity analysis was not conducted in this study, and the stability of the results could not be determined. Nevertheless, the overall quality of the literature in this study is relatively high, so the conclusions obtained still have certain clinical reference value. Finally, sensitivity analysis was not carried out in this study, and the stability of the results could not be judged. Nevertheless, the overall quality of those studies were high with NOS standards, so the conclusions still had certain clinical reference value.

5. Conclusion

Patients with ABBI had poor prognosis and high mortality; the risk factors of death were complicated. Identifying controllable related factors and intervening would have a positive effect on reducing the mortality of the patients. In summary, the severity of the patient's age, APACHE II, underlying disease, using of hormones and immunosuppressants, and various invasive operations were the main risk factors for high mortality. In clinical work, it was necessary to focus on older patients, dynamically monitor the APACHE II score, carefully evaluate the effect of hormone and immunosuppressant application, and strictly control the indications of invasive operation or treatment, as to effectively prevent ABBI, improve the prognosis and reduce the mortality in patients.

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