CLINICAL AND LABORATORY FEATURES RELATED TO MORTALITY RATE OF BLOOD STREAM INFECTION PATIENTS ADMITTED TO NATIONAL HOSPITAL FOR TROPICAL DISEASES (7/2017 - 6/2020)

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Summary

Objectives: The aim of this study was to evaluate clinical and laboratory features related to mortality rate of blood stream infection patients admitted to National hospital for Tropical Diseases. *Subjects and methods:* A cross - sectional study was conducted among patients diagnosed blood stream infection from 7/2017 to 6/2010 in National hospital for Tropical Diseases. A total of 200 patients with clinical sign, symptoms of sepsis and positive blood culture were included in the study. Univariate and multivariate logistic regressions were used to identify independent prognostic factors for mortality. *Results:* Of 200 blood stream infection patients, 131 patients were male (65.5%); 150 patients (75%) had comorbidities, the most common diseases are cardiovascular diseases (26%), diabetes mellitus (23.5%), hepatic diseases (18.5%) and alcoholism (13%). *E. coli* (32%), *S.aureus* (28.5%) are the most frequent causes indentified in blood culture. There were 44 died (22%) and 156 survived (78%). Platelet < 100G/L (OR = 3.61), rAPTT > 1.25 (OR = 6.26), shock (OR = 71.99), the number of organ dysfunctions ≥ 3 (OR = 4.06) were independent prognostic factors. *Conclusion:* Septic shock, multiple organ failure and thrombocytopenia are the prognostic factors for mortality of blood stream infection. It should be early detected in blood stream infection for intervention.

Key words: Blood stream infection, mortality, prognostic factors.

BACKGROUND

Blood stream infection (BSI) is a major healthcare problem that cause mortality and morbidity worldwide. Despite extensive investigation in diagnosis, treatment and prognosis in recent decades, the burden of bloodstream infection has not been well resolved[1,3].

In patients with BSI, an increasing number of organ dysfunction is correlated with severity and mortality. When BSI reached the stage of irreversible septic shock, multiorgan failure, resuscitation became ineffective. As a result, diagnose and prognosis for patients in early stage plays a vital role to detect and treat BSI, contributing to reduce mortality rate, shortening the length of stay[4]. Furthermore, early interventions, especially early appropriate antimicrobial therapy in first hour of hypotension, were associated with a survival rate of 79.9%, and each hour of delay was associated with an average decrease in survival of 7.6%[5].

Although there were a large number of studies that were conducted to determine prognostic factors of bloodstream infection, the results were still inconsistent.

This study was conducted to evaluate clinical and laboratory features related to mortality of blood stream infection patients admitted to National Hospital for Tropical Diseases from 2017 to 2020.

SUBJECTS AND METHODS

Study area, study design and study population: A retrospective and prospective cross-sectional study was

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conducted among all admitted patients with blood stream infection at National hospital of Tropical Diseases from 7/2017 to 6/2010.

Inclusion criteria: Patients were enrolled in the study if they meet both of two inclusion criteria (a and b) below:

Clinical symptoms:

- Have two or more of SIRS criteria: (1) Temperature > 38°C or < 36°C; (2) Heart rate > 90beats/min; (3) Respiratory rate > 20breaths/minor $PaCO_2$ < 32mmHg (without support); (4) White blood cells > 12000 or < 4000/mm^3, orbandemia > 10%.

- Or clinical symptoms suggested sepsis such as fever, more than one site of infection, symptoms of reticuloendothelial system reaction such as splenomegaly, hepatomegaly, adenomegaly.

Blood culture: The bacteria was identified in the blood culture. The blood sample was collected within 48 hours since admission.

Exclusion criteria: Patients under 18 years old; pregnant patients; patients positive with HIV; patients with history of chronic kidney failure or liver failure; blood samples for culture was collected after admission 48 hours.

Data collection and laboratory method: After eligible patients were enrolled in the study, blood sample was collected and sent to the medical microbiology laboratory for culture. Bacteria were identified by using Vitek and Maldi biotyper.

The clinical and laboratory data were collected with CRF.

Data analysis and interpretation: Patients were categorized into 2 groups based on outcome: death and survival, univariate and multivariate logistic regressions were used to identify independent prognostic factors for mortality.

Statistical analysis: calculating mean and standard deviation (SD) of quantitative variables, percentage of qualitative variables, using χ^2 test, Fisher exact test, t - test student, Mann Whitney U test, level of statistical significance p < 0.05 (two - sided asymptote). Using SPSS 20 software to analyze data.

RESULTS

From 6/2017 - 6/2020, 200 patients were enrolled in the study. There was 131 male patients (65.5%) and 69 female patients (34.5%), male/female ratio was 1.9/1. The average age was 57.8 ± 16.2 years. Of them, 150 patients (75%) had comorbidities, the most common disease was cardiovascular diseases (26%), diabetes mellitus (23.5%), hepatic diseases (18.5%), alcoholism (13%). Gram - negative bacteria accounted for 61.5%, gram - positive bacteria accounted for 38.5%. The most frequently met bacteria was *E. coli* (32%) and *S. aureus* (28.5%).

There were 156 patients in survival group (78%), 44 patients were in death group (22%). The average length of stay was 14.3 ± 9.1 days, the average time to onset of shock was 6.4 ± 6.9 days and the average time to appropriate antimicrobial therapy was 0.7 ± 1.5 days.

Table 1. Characteristics of age, sex, comorbidities, bacteria, outcomes and time factors

Variables	n	%
Age (years)	**57.8 ± 16.2**	
Sex		
Male	131	65.5
Female	69	34.5
Comorbidities	150	75
Hepatic diseases	37	18.5
Alcoholism	26	13.0
Corticosteroid long - term use	11	5.5
Diabetes mellitus	47	23.5
Cardiovascular diseases	52	26.0
Gout	6	3.0
Cancer	5	2.5
Hematologic diseases	2	1.0
Others*	40	20
Microbiological documentation		
Gram - positive bacteria	**77**	**38.5**
S. aureus	57	28.5
S. suis	7	3.5
S. pneumoniae	4	2
Others	9	4.5
Gram - negative bacteria	**123**	**61.5**
E. coli	64	32
K. pneumonia	20	10
S. maltophilia	8	4
Salmonella spp	6	3
Others	25	12.5
Outcomes		
Died	44	22
Survived	156	78
Time factors (days)		
Length of stay	14.3 ± 9.1	
Time to onset of shock	6.4 ± 6.9 (n=29)	
Time to appropriate antimicrobial therapy	0.7 ± 1.5 (n=170)	

**Others: COPD, asthma, nephrolithiasis, cholelithiasis, etc.*

Clinical and paraclinical disorders in first 24 hours related to death

Table 2. Hematocytology and coagulation in first 24 hours related to death

Variables	Death (n.%)	Survival (n.%)	%
Hemoglobin (g/l)			
≥ 120	18 (17.8)	83 (82.2)	0.129
<120	26 (26.8)	71 (73.2)	
White blood cells (G/l)			
≥ 10	116 (81.7)	26 (18.3)	0.064
4 - 10	14 (29.8)	33 (70.2)	
<4	4 (44.4)	5 (55.6)	
Platelet (G/l)			
≥ 100	15 (11.5)	115 (88.5)	**< 0.001**
< 100	29 (42.6)	39 (57.4)	
Coagulation			
PT%	55.2 ± 25.4	73.2 ± 22.2	**< 0.001**
INR	1.8 ± 0.8	1.3 ± 0.5	**< 0.001**
APTT(s)	53.8 ± 29.3	36.2 ± 10.3	**< 0.001**
rAPTT	1.7 ± 0.9	1.2 ± 0.4	**0.003**
Fibinogen (g/l)	4.5 ± 2.4	5.3 ± 1.9	0.070
D - Dimer (µg/l)	12659 ± 15654	5891 ± 7979	**0.014**

Comments: The result showed that anaemia (Hb < 120g/l) and thrombocytopenia (platelet < 100G/l) were related to mortality (p < 0.001). Change in white blood cell count made no difference between death and survival group.

There was a significant difference of PT%, INR, APTTs, rAPTT and D - dimer between two groups with p < 0.05.

Table 3. Hepatology and nephrology disorders in first 24 hours related to death

Variables	Death (n.%)	Survival (n.%)	%
Bilirubin (µmol/l)			
> 34	17 (41.5)	24 (58.5)	**0.039**
≤ 34	23 (23.9)	73 (76.1)	
Albumin (g/l)			
≥ 35	7 (15.6)	38 (84.4)	**0.018**
< 35	30 (35.3)	55 (64.7)	
AST (U/l)			
≥ 40 U/l	33 (27.7)	86 (72.3)	**0.038**
< 40 U/l	11 (14.9)	63 (85.1)	
ALT (U/l)			
≥ 40 U/l	24 (24.5)	74(75.6)	0.528
< 40 U/l	17 (18.9)	73 (81.1)	
Ure (mmol/l)			
≥ 7.5	33 (38.4)	53 (61.6%)	**< 0.001**
< 7.5	11 (10.6)	93 (89.4)	
Creatinin (mmol/l)			
≥ 120	26 (40)	39 (60)	**< 0.001**
< 120	18 (13.6)	114 (86.4)	

Comments: The result showed that there was statistically significant difference inthe propotion of patients had > 34µmol/l, albumin < 35g/l, AST < 40U/l, ure ≥ 7.5mmol/l and creatinin ≥ 120mmol/l between death group and survival group.

Table 4. Evaluate diagnostic value of clinical and laboratory findings in first 24 hours (univariate logistic regression analysis)

Factors	P	OR	95% CI (OR)
Age	0.168	0.99	0.97 - 1.01
Male gender	0.672	0.86	0.42 - 1.75
History of diabetes	0.791	1.111	0.51 - 2.42
History of cirrhosis	0.415	1.41	0.62 - 3.18
Glasgow < 15	**< 0.001**	**8.05**	**3.70 - 17.55**
MAP < 70 mmHg	**< 0.001**	**2.64**	**1.28 - 5.46**
Heart rate ≥ 120 beats/min	**< 0.001**	**5.03**	**2.10 - 12.08**
Temperature > 38°C	0.557	1.25	0.60 - 2.62
Respiratory rate ≥ 22 breaths/min	**< 0.001**	**1.21**	**1.10 - 1.32**
Hb < 100g/l	**0.030**	**2.39**	**1.09 - 5.24**
WBC < 4G/l	0.116	2.98	0.76 - 11.61
Platelet< 100G/l	**< 0.001**	**5.70**	**2.77 - 11.73**
Bilirubin > 34µmol/l	**0.041**	**2.25**	**1.03 - 4.90**
Albumin < 35g/l	**0.02**	**2.96**	**1.18 - 7.44**
Ure ≥ 7.5mmol/l	**< 0.001**	**5.26**	**2.46 - 11.27**
Creatinin ≥ 120µmol/l	**< 0.001**	**4.22**	**2.09 - 8.52**
INR > 1.5	**0.001**	**3.78**	**1.70 - 8.44**
rAPTT > 1.25	**< 0.001**	**3.75**	**1.60 - 8.81**
D - dimer > 2400µg/l	**0.049**	**3.39**	**1.00 - 11.51**
Shock	**< 0.001**	**117.44**	**37.06 - 372.18**
Number of organ dysfunctions ≥ 3	**< 0.001**	**9.62**	**4.51 - 20.51**
Multilobar pneumonia	**< 0.001**	**5.94**	**2.48 - 14.23**

Comments: By using univariate logistic regression analysis, Glasgow < 15 (OR = 8.05), MAP (OR = 2.64), heart rate ≥ 120 beats/min (OR = 5.03), respiratory rate ≥ 22 breaths/min (OR = 1.21), hemoglobin < 100g/L (OR = 2.39), platelet < 100G/L (OR = 5.7), bilirubin > 34µmol/L (OR = 2.25), albumin < 35g/l (OR = 2.96), ure ≥ 7.5mmol/l (OR = 5.26), creatinin ≥ 120µmol/L (OR = 4.22) , INR > 1.5 (OR = 3.78), rAPTT > 1.25 (OR = 3.75), D - dimer > 2400 (OR = 3.39), shock (OR = 117.44), number of organ dysfunctions ≥ 3 (OR = 9.62) and multilobar pneumonia (OR = 5.94) were prognostic factorsof blood stream infection, level of statistical significance p < 0.05.

Table5. Prognostic factors (multivariate logistic regression analysis)

Factors	P	OR	95% CI (OR)
Glasgow < 15	0.099	2.78	0.82 - 9.37
MAP < 70mmHg	0.07	0.23	0.05 - 1.15
Heart rate ≥ 120 beats/min	0.81	0.79	0.11 - 5.47
Respiratory rate ≥ 22 breaths/min	0.63	0.71	0.18 - 2.80
Hemoglobin < 100 g/L	0.17	2.47	0.68 - 8.99
Platelet < 100G/L	**0.02**	**3.61**	**1.18 - 11.01**
Bilirubin > 34µmol/L	0.16	2.51	0.70 - 9.04
Albumin < 35g/l	0.24	2.45	0.55 - 10.98
Ure ≥ 7.5mmol/L	0.39	1.84	0.47 - 7.22
Creatinin ≥ 120µmol/L	0.81	1.18	0.29 - 4.76
INR > 1.5	0.64	1.41	0.33 - 6.00
rAPTT > 1.25	**0.03**	**6.26**	**1.19 - 33.02**
D-dimer > 2400µg/l	0.38	2.44	0.34 - 17.46
Shock	**0.000**	**71.99**	**21.69 - 238.91**
Number of organ dysfunctions ≥ 3	**0.02**	**4.06**	**1.24 - 13.34**
Multilobar pneumonia	0.499	1.65	0.39 - 7.08

Comments: The significant prognostic factors of table 4 were analysed using multivariate logistic regression to find out correlation and independent prognostic factors. The result showed that, platelet < 100G/L (OR = 3.61), rAPTT > 1.25 (OR = 6.26), shock (OR = 71.99), the number of organ dysfunctions ≥ 3 (OR = 4.06) were independent prognostic factors (p < 0.05). Glasgow < 15, hemoglobin < 100g/L, albumin < 35g/l, D - dimer > 2400µg/l produced a 2.78 - fold; 2.47 - fold, 2,45 - fold; 2.44 - fold increase in mortality rate, respectively, nevertheless, there is no statistical significance with p > 0.05.

DISCUSSION

Characteristics of blood stream infection patients: Our study showed that, average age of patient was 57.8 ± 16.2 years, lower than Zanon's study at Brazil (60.7 ± 18.6) and Jong Won Kim's study (69.3 ± 14.2). There was 131 male patients (65.5%); 150 patients (75%) had comorbidities, the most common diseases are cardiovascular diseases (26%), diabetes mellitus (23.5%), hepatic diseases (18.5%) and alcoholism (13%). Underlying diseases need to be carefully assessed to make the appropriate treatment decision. Gram - negative bacteria accounted for 61.5%, being much higher than gram - positive bacteria (38.5%). A study of Khanh N.T.M in 100 blood stream infection patients admitted to NHTD from 9/2013 to 10/2014 showed similar result: 62.1% gram - negative bacteria and 37.9% gram - positive bacteria. In our study, *E. coli* (32%), *S. aureus* (28.5%) and *K. pneumoniae* (10%) are the most frequent causes indentified in blood culture. On the other hand, this result is different with the Brian C. Pien's study which was done in American. In the Brian C. Pien's study, the most frequent causes are S.aureus (25.3%), *E. coli* (13.7%), *Enterococcus spp.* (10,3%) and *Klebsiella pneumoniae* (9.5%). Although the rates of each isolated bacteria differ from study to study, the two most common causes of bloodstream infection are *E. coli* and *S. aureus.* The average length of stay was 14.3 ± 9.1, the average time to onset of shock was 6.4 ± 6.9 and the average time to appropriate antimicrobial therapy was 0.7 ± 1.5. Mortality rate of sepsis in our study was high (22%), which was lower than in Zanon's study (31.1%) and similar to Brian C. Pien's study (20%)[6,7] and Khanh N.T.M's study (24.5%)[8].

Prognosis factors of sepsis: Orclinical symptoms suggested sepsis such as fever, more than one site of infection, symptoms of reticuloendothelial system reaction such as splenomegaly, hepatomegaly, adenomegaly. Sepsis is a major healthcare problem, affecting millions of people around the world each year. Therefore, determination of prognostic factors plays an important role to improve outcome of sepsis. Although there were a large number of researches determined independent prognostic factors of sepsis, the results were inconsistent. A study of Brian C.Pien on 1706 sepsis patients showed that elderly, hypotension, leukopenia, cancer and renal failure were independent prognostic factors[7]. Besides, Jong Won Kim's study showed that elderly, leukopenia, elevated INR and hypoxia were prognostic factors[9,10].

In Vietnam, a study of Pham Thi Ngoc Thao at Choray hospital's ICU department pointed out the number of organ dysfunction, uremia, arterial blood pH and HCO3 were significant related to mortality[4].

Our study showed that, there was statistically significant difference in coagulation factors (platelet, PT%, INR, APTTs, rAPTT and D - dimer) and hepatology and nephrology disorders between survival group and death group.

By using univariate and multivariate logistic regression analysis, we found out independent prognostic factors of sepsis: platelet < 100G/L, rAPTT > 1.25, shock, the number of organ dysfunctions ≥ 3 which increased

mortality rate 3.61 times, 6.26 times, 71.99 times and 4.06 times, respectively. Coagulation disorders were common in blood stream infection, ranging from hypercoagulation to disseminated intravascular coagulation. Paola Saracco found that coagulation disorder were an independent prognostic factor for patient death. Besides, septic shock is a prognostic factor of mortality, a turning - point of sepsis development that increased mortality rate 71,99 times. Patients with bloodstream infection often had multiorgan dysfunction. Harbarth's study was also point out the number of organ dysfunctions was an independent prognostic factor[9].

In our study, Glasgow < 15, hemoglobin < 100g/L, albumin < 35g/l, D - dimer > 2400µg/l increased mortality rate with OR = 2.78; OR = 2.47; OR = 2,45; OR = 2.44 respectively. Nevertheless, in multivariable logistic regression analysis, these factors are not independent in sepsis prognosis.

CONCLUSION

In our study, the proportions of elderly patients, male patients and patients with comorbidities were high. The mortality rate was high (22%) and the most common indentified bacteria was gram - negative bacteria; *E. coli* and *S. aureus* were the predominant causes met in blood culture. Platelet < 100G/L (OR = 3.61), rAPTT > 1.25 (OR = 6.26), shock (OR = 71.99), the number of organ dysfunctions ≥ 3 (OR = 4.06) were independent prognostic factors. Besides, length of stay was the time factor that had prognostic value.

REFERENCES

1. ClaudioViscoli et al. Bloodstream Infections: The peak of the iceberg. *Virulence.* 2018;7(3):248-251.

2. Kevin B.Laupland, Deirdre L. Church, et al. Population-Based Epidemiology and Microbiology of Community-Onset Bloodstream Infections. *Clinical Microbiology Reviews.* 2014;27(4):647-664.

3. Angus D, Linde-Zwirble W, Lidicker J, Clermont G, Carcillo J, Pinsky M. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001;29(7):1303-1310.

4. Pham Thi Ngoc Thao. Clinical, testingand prognostic value of cytokinsof severe sepsis patients. *Doctor of Medicine thesis.* 2013

5. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.

6. Zanon F, Caovilla JJ, Michel RS, et al. Sepsis in the intensive care unit: etiologies, prognostic factors and mortality. *Rev Bras Ter Intensiva.* 2008;20(2):128-134.

7. Brian C., Punidha, Natalia, et al. The Clinical and Prognostic Importance of Positive Blood Cultures in Adults. *The American Journal of Medicine.* 2010;123(9):819-828.

8. Khanh N.T.M, et al. Value of the inflammatory markers in the prognosis of sepsis in patients treated at the National hospital for Tropical Diseases (9/2013 - 10/2014). *Vietnam Journal of Infectious diseases.* 2017;5(5): 36.

9. Harbarth Stephan, et al. Epidemiology and Prognostic Determinans of Bloodstream Infections in Surgical Intensive Care. *Archives of Surgery.* 2002;137(12): 1353.

10. Kim Jong Won, Kim Jin Joo, et al. The Prognostic Factors of Pneumonia with Septic Shock in Patients Presenting to the Emergency Department. *Korean Journal of Critical Care Medicine.* 2015;30(4): 258-264.