Blood Culture Evaluation for Carbapenem Exposure in Pyogenic Liver Abscess: A Two-Center Retrospective Study

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Abstract

Background: High antibiotic consumption in pyogenic liver abscess (PLA) is unnecessary. Using the databases of two centers, we retrospectively evaluated the effects of blood culture on the exposure to carbapenems in patients with PLA.

Methods: All patients diagnosed with PLA at two comprehensive tertiary care centers from 2014 to 2020 were assessed. Demographics and clinical data were analyzed, and multiple regression analysis was performed to investigate the association between blood culture and exposure to carbapenems after controlling for potential confounders.

Results: Blood culture results were available in 110 (46.0%) patients, of whom 44 (40.0%) patients were tested positive on bacterial culture. The blood culture positivity rate was significantly higher in the sepsis subgroup than in the non-sepsis subgroup (58.1% vs. 32.9%, P = 0.015). The number of patients receiving carbapenems in the blood culture cohort was significantly lower than that in the other cohort (19.1% vs. 31.8%, P = 0.026). Multivariate analysis showed that patients in the blood culture group were less likely to be treated with carbapenems for >5 days than those in the unavailable blood culture group (adjusted OR = 0.33, 95% CI: 0.16–0.68, P=0.003), especially those in the sepsis subgroup (adjusted OR = 0.17, 95% CI: 0.05–0.53, P = 0.002).

Conclusion: Blood culture might be associated with less carbapenem exposure, particularly in PLA complicated with sepsis. More attention should be paid to early blood cultures in the emergency setting.

1. Introduction

Pyogenic liver abscess (PLA) is a common infectious disease in the emergency department and its prevalence has increased steadily in China in recent years [1, 2]. With the widespread use of antibiotics and development of imaging technology and drainage techniques, the mortality rate associated with PLA is slowly declining. PLA is often complicated by sepsis, and according to the current guidelines, adequate antibiotic therapy should be administered as soon as possible, ideally within 1 hour[3]. The initial choice of antibiotic is usually based on empirical evidence only. Therefore, emergency clinicians tend to administer wide-spectrum antibiotics since results of microbiological cultures are not available. However, unwarranted exposure to antibiotics, especially carbapenems, inevitably leads to antibiotic resistance, resulting in adverse effects and high costs. Targeted antibiotic therapy for the causative pathogen can effectively reduce these associated complications.

Blood cultures can detect pathogenic bacteria in patients with PLA. They are considered the most sensitive method for detecting bacteremia and commonly performed for patients with fever, chills, leukocytosis, focal infections, and sepsis [4]. However, the application of blood culture in the emergency department is limited owing to a low positivity rate and the large amount of sample needed (typically 40–50 ml). Therefore, some researchers have suggested that blood cultures should not be performed for adult patients with isolated fever or leukocytosis without considering the pretest probability [5]. However,

some scholars argue that performing cultures after administration of antibiotics diminishes their sensitivity and clinical utility [6]. In a previous study, blood culture positivity in PLA (3–6 cm) was approximately 28% [7]. Therefore, we hypothesized that blood culture results can help in scientific and rational medical decision making for antimicrobial de-escalation strategies.

Thus far, limited studies have evaluated the relationship between performing blood culture and carbapenem use in PLA. Therefore, this study aimed to evaluate the prevalence of extended-spectrum beta-lactamase (ESBL)-producing isolates and the relationship between performing blood culture and the exposure to carbapenems.

2. Materials And Methods

2.1 Study design and patients

This retrospective cohort study was conducted at two comprehensive tertiary care centers in Shanghai that had 604 and 2090 beds. All adult patients with PLA who visited the emergency department from January 2014 to March 2020 were enrolled. Patients with carbapenem allergy; patients with a hospital stay < 5 days; those with other invasive infections requiring carbapenem administration on admission; those with amoebic liver abscess, fungal liver abscess, or hydatid secondary liver abscesses; those who were transferred to another hospital; and those with insufficient clinical data were excluded from the study (Fig. 1). The study was approved by the ethics committee of the both the hospitals. Owing to the retrospective nature of the study, the requirement for informed consent was waived.

2.2 Data collection and variable definitions

The medical records of all patients who had been discharged from the two centers with a diagnosis of PLA defined by the International Classification of Disease, 10th Revision code K75.0 were reviewed from January 2014 to March 2020.

Anonymized patient data were collected by two trained observers using a prespecified case report form. Data on demographic characteristics, coexisting disease, clinical presentations, laboratory findings, radiological findings, microbiologic data, antibiotics data, complications, and clinical outcomes were reviewed.

Hepatobiliary benign diseases included fatty liver disease, hepatitis, liver cirrhosis, biliary stone diseases, and biliary tract inflammation. Hepatobiliary malignant diseases included hepatocellular carcinoma and cholangiocarcinoma. Abdominal surgery history included cholecystectomy, biliary tract surgery, gastrointestinal surgery, hepatectomy, gynecologic surgery, and pancreatic surgery. Clinical presentations included symptoms at admission and changes during hospitalization, such as daily body temperature. Laboratory findings included hematologic and biochemical findings. Radiological findings, including abscess size, number, and location, were assessed using abdominal ultrasonography, computed tomography, or magnetic resonance image. Microbiological data included time of blood culture, time of

the oral preliminary report, time of blood culture results, microbial strain, and ESBL positivity. Data on antibiotics included antibiotic type (such as cephalosporins, piperacillin/tazobactam, metronidazole, quinolones, glycopeptides, and carbapenems), antibiotic dose and course, reasons for antibiotic changes, and adjusted regimens. Carbapenem use was defined as continuous exposure to carbapenems for > 5 days. Since microbial sensitivity testing results were usually obtained within 6 days (> 95% blood culture and drug sensitivity results were officially reported on day 6 of ordering the culture in our study), the antimicrobial regimen was subsequently maintained or adapted according to the results. The severity of illness on admission was evaluated with the Sequential Organ Failure Assessment (SOFA) scoring system in the first 24-hour on admission. The complications included sepsis and sepsis shock based on the Sepsis-3 definition [8]. Clinical outcomes included the following: (a) in-hospital mortality, defined as PLA-related mortality in hospital; (b) length of hospitalization, defined as the number of days of hospital stay; (c) clinical recovery, defined as the number of days until the body temperature returned to < 37.3 °C or symptomatic improvement after discharge.

2.3 Blood culture

Aerobic and anaerobic cultures were performed for the blood samples. Species identification and antimicrobial susceptibility were tested using VITEK automated systems (bioMérieux Vitek, Hazelwood, MO, USA) and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria.

Blood culture results were classified as positive or negative based on the presence or absence of bacterial growth, respectively. The provisional oral report was provided to clinicians immediately after obtaining strain staining results (usually the next day). Blood culture positivity was defined as the detection of a microbiological pathogen within 6 days of incubation. The results of blood culture showing presence bacterial growth were considered negative if the microbiological pathogen could not be identified. Each positive blood culture result was assessed for contamination (false positivity) according to the established criteria [9]. Thereafter, all false-positive culture results were coded as negative.

Phenotypical confirmation of ESBL detection and susceptibility to ESBL-positive isolates were evaluated using the disk diffusion technique in our clinical microbiology laboratories, as recommended by the CLSI.

2.4 Statistical analysis

Data are presented as number (%) for categorical variables and as mean and standard deviation or median (interquartile range) for continuous variables with normal distribution and non-normal distribution, respectively. The independent Student’s t-test or nonparametric Mann–Whitney test was used to analyze continuous variables, and the Pearson’s chi-square test or Fisher’s exact test was used for categorical variables. Normality was tested using the Shapiro–Wilk test.

Univariate and multivariate logistic regression analyses were performed to identify significant factors related to carbapenem prescription in patients with PLA. Stratified analyses were performed based on whether PLA was complicated with sepsis. Clinically relevant variables and those with P-values < 0.10 in the univariate analyses were included in the multivariable logistic regression model[10, 11]. The odds

ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using the logistic regression model. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Demographic and clinical characteristics

In total, 272 patients with PLA were admitted to the two hospitals from January 2014 to March 2020. Of them, 239 patients with PLA were included. Blood culture results were available in 110 (46.0%) patients (blood culture group); the remaining patients in whom the blood culture results were unavailable were included in the unavailable blood culture group. In the blood culture group, the mean patient age was 63.1 years and 56.4% patients were males. There were statistically significant differences in coexisting diseases such as diabetes mellitus, hepatobiliary benign disease, and abdominal surgery history between the groups. Fever was the most common symptom, followed by abdominal pain. There were no differences in symptoms at presentation, abscess characteristics, SOFA scores, sepsis, or septic shock between the groups. However, the blood culture group had a lower C-reactive protein (CRP) level than the unavailable blood culture group (107.2 ± 63.8 vs. 130.3 ± 59.7 mg/L, $P = 0.004$).

Carbapenems were administered less frequently in the blood culture group than in the unavailable blood culture group (21 [19.1%] vs. 41 [31.8%] patients, $P = 0.026$). The use of other antibiotics and combination therapy with antibiotics was similar between the groups. Most patients (182/239, 76.2%) had received combination therapy with antibiotics. The length of hospitalization was significantly shorter in the blood culture group than that in the unavailable blood culture group (15.0 [inter-quartile range (IQR): 13.0–22.0) vs. 13.0 [IQR: 9.0–19.0] days, $P < 0.001$). Most patients (230/239, 96.2%) recovered, while nine (3.8%) patients died in the hospital. Four patients died of severe general sepsis or septic shock, three died of cachexia and subsequent multiple organ failure, one died of inadequate antibiotic coverage, and the one died of severe hypertonic hyperglycemic syndrome. However, there was no difference in mortality or clinical recovery between the groups (Table 1).

Table 1
Baseline characteristics with and without blood culture

Variables	Unavailable Blood Culture (N = 129)	Blood Culture (N = 110)	P-value
Age, mean ± SD (years)	64.3 ± 13.3	63.1 ± 13.4	0.492
Gender (male), n (%)	73 (56.6%)	62 (56.4%)	0.972
Coexisting diseases, n (%)			
Diabetes mellitus	62 (48.1%)	68 (61.8%)	0.033
Hepatobiliary benign disease	39 (30.2%)	49 (44.6%)	0.022
Underlying malignancy	9 (7.0%)	10 (9.1%)	0.547
Abdominal surgery history	16 (12.4%)	27 (24.6%)	0.015
Symptoms on admission, n (%)			
Fever (BT > 37.3 °C)	118 (91.5%)	98 (89.1%)	0.534
Abdominal pain	37 (28.7%)	37 (33.6%)	0.409
General Weakness	25 (19.4%)	21 (19.1%)	0.955
Abscess location, n (%)			0.449
Right lobe	93 (72.1%)	87 (79.1%)	
Left lobe	29 (22.5%)	19 (17.3%)	
Both lobes	7 (5.4%)	4 (3.6%)	
Abscess number, n (%)			0.054
Solitary abscess	106 (82.2%)	99 (90.8%)	
Multiple abscess	23 (17.8%)	10 (9.2%)	
Average size of abscess (cm)	5.9 ± 2.4	6.1 ± 2.8	0.515
Laboratory findings			
Leucocytes ($\times 10^9$/L)	11.4 ± 5.1	10.3 ± 4.3	0.063
C-reactive protein (mg/L)	130.3 ± 59.7	107.2 ± 63.8	0.004
Procalcitonin (ng/ml)	4.3 (0.5–11.6)	5.0 (0.4–9.8)	0.759
Time of oral preliminary blood culture report (days)	NA	1.0 ± 0.2	NA
Time of blood culture result (days)	NA	6.0 ± 0.5	NA

NA: not applicable

Variables	Unavailable Blood Culture (N = 129)	Blood Culture (N = 110)	P-value
Positive Blood Culture rate, n (%)	NA	44 (40.0%)	NA
Positive ESBL rate, n (%)	NA	8 (7.3%)	NA
SOFA scores	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.589
Sepsis, n (%)	36 (27.9%)	31 (28.2%)	0.962
Septic shock, n (%)	7 (5.4%)	2 (1.8%)	0.144
Antibiotics treatment, n (%)			
Cephalosporins	118 (91.5%)	99 (90.0%)	0.695
Piperacillin/tazobactam	7 (5.4%)	4 (3.6%)	0.510
Quinolones	45 (34.9%)	39 (35.5%)	0.927
Metronidazole	48 (37.2%)	30 (27.3%)	0.102
Glycopeptides	4 (3.1%)	4 (3.6%)	0.819
Carbapenems	41 (31.8%)	21 (19.1%)	0.026
Antibiotics option, n (%)			0.325
Combined	95 (73.7%)	87 (79.1%)	
Single	34 (26.4%)	23 (20.9%)	
In-hospital mortality, n (%)	5 (3.9%)	4 (3.6%)	0.923
Length of hospitalization (days)	15.0 (13.0–22.0)	13.0 (9.0–19.0)	< 0.001
Clinical recovery (days)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	0.794
NA: not applicable			

3.2 Microbiological characteristics

Of the 110 patients in the blood culture group, 44 (40.0%) patients tested positive on bacterial culture. Of whom, 8 (7.3%) patients were tested positive for an ESBL strain. The mean time for obtaining the oral preliminary blood culture report was 1.0 day, and the mean time to obtain the blood culture result was 6.0 days (Table 1). *Klebsiella pneumonia* (32/44 patients, 72.7%) was the most common pathogen cultured, followed by *Streptococcus* spp. (4/44 patients, 9.1%). Four (9.1%) patients had polymicrobial infection, while 40 (90.9%) patients had monomicrobial infection. Furthermore, the blood culture positivity rate was significantly higher than in the sepsis subgroup than in the non-sepsis subgroup (58.1% vs. 32.9%, P = 0.015) (Table 2).

Table 2
Microbiological characteristics in blood culture group

Organism cultured, n (%)	Blood culture (N = 110)		P-value
	Sepsis (N = 31)	Non-sepsis (N = 79)	
Positive	18 (58.1%)	26 (32.9%)	0.015
Klebsiella pneumonia	12 (66.7%) *	20 (76.9%) *	0.453
Streptococcus spp.	3 (16.7%) *	1 (3.9%)	0.146
Staphylococcus spp.	1 (5.6%) *	1 (3.9%)	0.789
Escherichia coli	1 (5.6%)	2 (7.7%)	0.782
Enterococcus spp.	1 (5.6%)	1 (3.9%) *	0.789
Enterobacter spp.	1 (5.6%)	2 (7.7%) *	0.782
Pseudomonas aeruginosa	1(5.6%) *	1 (3.9%)	0.789
ESBLs positive	4 (12.9%)	4 (5.1%)	0.154
Monomicrobial infection	16 (88.9%)	24 (92.3%)	0.698
Polymicrobial infection	2 (11.1%)	2 (7.7%)	0.698
Negative	13 (41.9%)	53 (67.1%)	0.015
*There were four cases of coinfection in the blood culture group.			

3.3 Significant factors related to carbapenem exposure according to univariate and multivariate analyses

Unavailable blood culture results, sepsis, high leucocyte count, and elderly age were associated with high carbapenem prescription rates (Table 3). Univariate analysis indicated that PLA with sepsis was associated with a high exposure to carbapenems (OR = 2.91, 95% CI: 1.58–5.38, P < 0.001) and that available blood culture was associated with a low exposure to carbapenems (OR = 0.50, 95% CI: 0.28–0.93, P = 0.026). After adjusting for the other significant predictors in the multiple regression model, patients with PLA in the blood culture group were less likely to be treated with carbapenems for > 5 days than those in the unavailable blood culture group (adjusted OR = 0.33, 95% CI: 0.16–0.68, P = 0.003), especially those in the sepsis subgroup (adjusted OR = 0.17, 95% CI: 0.05–0.53, P = 0.002) (Table 4).

Table 3
Univariate analysis for the factors related to carbapenems use

Variables	Carbapenems (N = 62)	Univariate analysis		
		Odds ratio	95% CI	P-value
Gender	33 (53.2%)	1.20	(0.60–2.14)	0.548
Diabetes mellitus, n (%)	31 (50.0%)	0.88	(0.49–1.58)	0.673
Hepatobiliary benign disease, n (%)	18 (29.0%)	0.60	(0.30–1.20)	0.141
Underlying malignancy, n (%)	5 (8.1%)	1.02	(0.35–2.96)	0.969
Abdominal surgery history, n (%)	7 (11.3%)	0.50	(0.21–1.19)	0.116
Abscess location, n (%)				0.692
Right lobes	45 (72.6%)	1.00		
Left lobes	13 (21.0%)	1.11	(0.54–2.29)	0.769
Both lobes	4 (6.5%)	1.71	(0.48–6.13)	0.407
Abscess number, n (%)				0.146
Solitary abscess	50 (80.7%)	1.00		
Multiple abscess	12 (19.3%)	1.77	(0.81–3.86)	0.150
Blood culture, n (%)	21 (33.9%)	0.50	(0.28–0.93)	0.026
Pus culture, n (%)	32 (51.6%)	0.77	(0.43–1.38)	0.384
ESBL positive rate, n (%)	8 (12.9%)	NA	NA	NA
Sepsis, n (%)	28 (45.2%)	2.91	(1.58–5.38)	< 0.001
Septic shock, n (%)	7 (11.3%)	3.21	(1.78–6.45)	< 0.001
Age (years)	67.0 ± 12.9	1.03	(1.00–1.05)	0.027
Abscess size (cm)	5.9 ± 2.6	0.97	(0.87–1.09)	0.631
Leucocytes (× 10^9/L)	12.5 ± 4.8	1.09	(1.03–1.16)	0.004
C-reactive protein (mg/L)	130.9 ± 61.9	1.00	(1.00–1.01)	0.103
Procalcitonin (ng/ml)	9.2 ± 11.2	1.01	(0.99–1.04)	0.416
NA: not applicable				

Table 4
Multivariate models for predicting carbapenems use and blood culture stratified by sepsis

Exposure	Model 1[a]		Model 2[b]		Model 3[c]	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Sepsis						
Blood Culture	0.29 (0.12–0.69)	0.005	0.29 (0.12–0.68)	0.005	0.17 (0.05–0.53)	0.002
Non-sepsis						
Blood Culture	1.01 (0.38–2.68)	0.982	1.03 (0.38–2.80)	0.952	0.65 (0.22–1.97)	0.451
Total						
Blood Culture	0.50 (0.28–0.93)	0.026	0.49 (0.26–0.91)	0.025	0.33 (0.16–0.68)	0.003
a: Unadjusted						
b: Adjusted for age and gender						
c: Adjusted for age, gender, leucocyte count, and C-reaction protein level, ESBL, biliary disease, gastrointestinal malignancy						

4. Discussion

This retrospective cohort study analyzed > 6-years data on patients with PLA from databases from two centers and found that performing blood cultures was associated with a low rate of carbapenem exposure in patients with PLA, especially in those with sepsis. The high blood culture positivity rate and the faster antibiotic degradation based on drug sensitivity results might play a role in explaining this correlation. To the best of our knowledge, this is the first study to evaluate the relationship between performing blood cultures and carbapenem exposure in patients with PLA. Some previous studies have reported the benefits of blood culture in many infectious diseases, although the results were slightly contradictory with the routine submission of blood cultures [6, 12, 13]. In this study, we summarized data from two emergency centers to help clinicians make decisions regarding the use of blood culture in the early stages of infection, in line with the current sepsis guidelines [4, 8]. current data support carbapenem-sparing options

The ESBL positivity rate of 8/110 (7.3%) observed in our study was lower than that reported in former studies [14]. We found majority of patients had more underlying diseases, recurrent episodes of infection, and broad-spectrum antibiotics exposure. PLA caused by ESBL-producing organisms from community-acquired infection is rare in China, which was consistent with the study by Lin et al. They also identified three specific genome regions in PLA strains; all PLA strains and non-invasive strains were ampicillin-

resistant and cefotaxime susceptible, and none were ESBL producing. They also suggested that ESBLs are not associated with PLA [15]. Furthermore, in our study, mortality rates in patients without microbiological evidence of infection were similar to those in patients with microbiological evidence of infection, which was similar to the results of previous studies [16, 17]. Therefore, we believe that it is not necessary to prescribe carbapenems for PLA patients with or without sepsis.

Blood cultures play a critical role in sepsis management and should be recommended for patients with sepsis [4]. Obtaining blood cultures during antibiotic therapy is associated with a significant low pathogen detection rate. To maximize utility, at least two sets of blood cultures should be obtained before initiating antibiotic therapy [18], which is consistent with the recent data reported by Dellinger et al.[19].

In our study, the general baseline characteristics were almost similar in blood culture and unavailable blood culture groups; however, clinicians preferred to order blood cultures in PLA patients with diabetes mellitus, hepatobiliary benign diseases, or abdominal surgery history. These differences could be attributable to PLA patients with coexisting diseases having become more common in hospitals, particularly since previous researches have demonstrated that diabetes mellitus results in an increased risk of PLA [20, 21]. Li et al. performed blood cultures for 118 patients with PLA and found that patients with diabetes mellitus were significantly more likely to have a positive blood culture result [21]. Furthermore, there was a significant difference in the CRP levels, possibly indicating that the severity of infection was higher in the blood culture group than in the other group, suggesting that clinicians tended to identify pathogens in cases where infection was considered severe.

The global spread of ESBLs has led to a significant increase in exposure of patients to carbapenems. Moreover, carbapenems are usually used as front-line drugs for gram-negative bacterial infections because of progressive resistance among other ESBLs. However, as documented in large surveillance studies, carbapenem resistance has been increasing [22]. Furthermore, there are significant variations in the usage of antibiotics and the ordering of blood cultures between hospitals and clinicians. Our work has contributed to the understanding of the relationship between performing blood cultures and carbapenem exposure. Multiple regression analysis was used to adjust many confounding factors and stratify patients with or without sepsis. Our study suggests that performing more blood cultures are associated with less exposure to carbapenems, which may help improve drug resistance.

However, our study has some limitations. First, the study was retrospective in nature, and procedures related to performing blood cultures with carbapenem administration were not standardized. However, this reflects the current real-world practice, especially in many developing countries, such as China. Second, carbapenem exposure is not well defined in the guidelines, and our results might have been affected by the culture time. Third, despite careful adjustment for several confounding factors, unmeasured confounders could have biased our results and the subsequent conclusions. Finally, strong conclusions cannot be made because the sample size was small and the results reported in two emergency medical centers in Shanghai cannot be extrapolated to other populations with different epidemiological or clinical settings.

5. Conclusion

In conclusion, blood culture is a useful method for detecting pathogenic bacteria and might reduce inappropriate carbapenem exposure, particularly in PLA complicated with sepsis. More attention should be paid to early blood cultures taken in the emergency care setting.

List Of Abbreviations

PLA
pyogenic liver abscess, ESBL:extended-spectrum beta-lactamase, OR:odds ratio, CI:confidence interval, SOFA:Sequential Organ Failure Assessment, CLSI:Clinical and Laboratory Standards Institute, CRP:C-reactive protein, IQR:inter-quartile range

Declarations

The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the funding agencies.

Ethics approval and consent to participate

It is a retrospective study based on data collected from patients' clinical records, approved by the Ethics Committee of the Shanghai Jiaotong University School of Medicine Affiliated with Renji and Xinhua hospitals. The data used in this study was anonymised before its use. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflict of interest.

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Authors' contributions

HW and LW collected all the clinical data; SH and JY were involved in statistical data analysis and editing the manuscript; ZW and YC designed the study. All authors read and approved the final manuscript.

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Figures

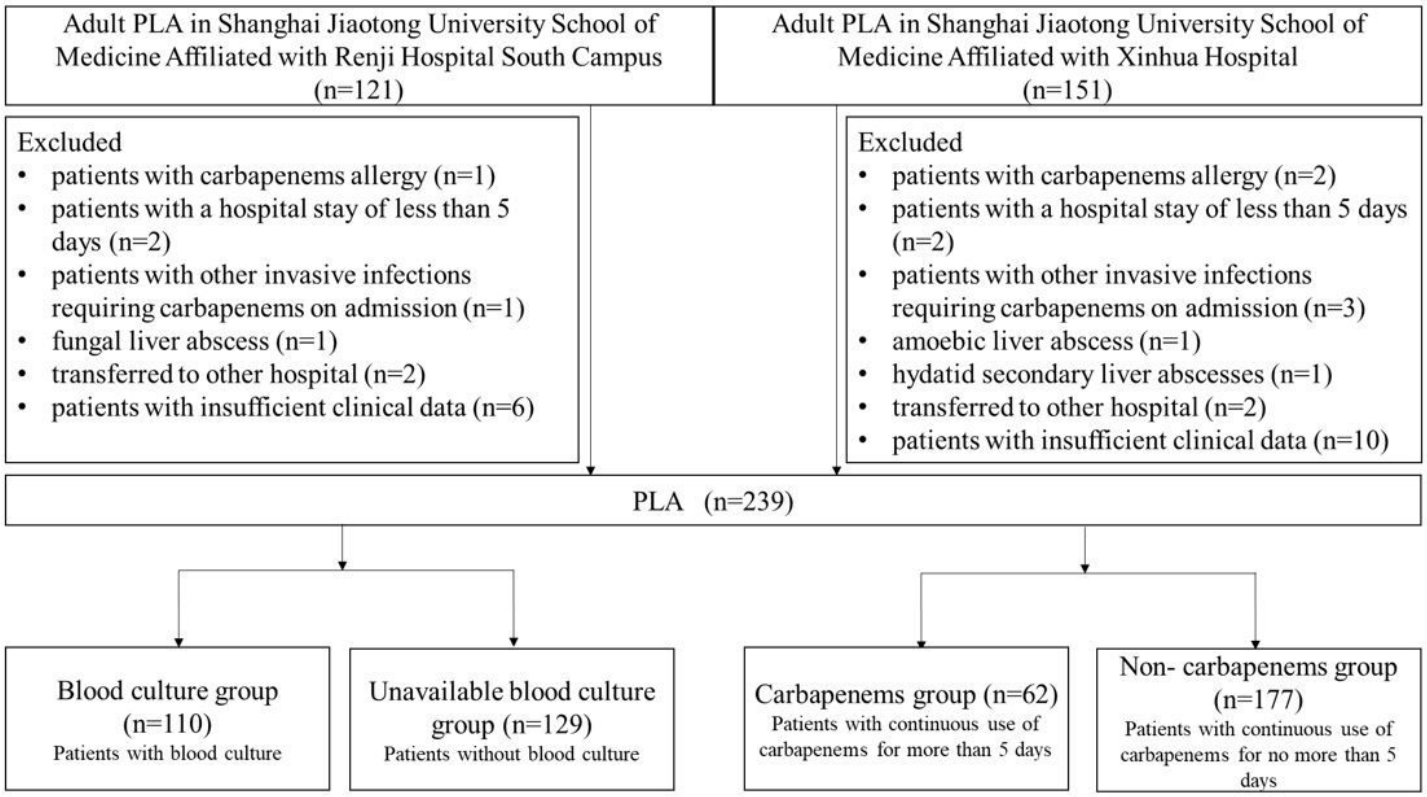

Figure 1

Flow chart of the patients with PLA enrolled in the study during Jan 2014 to Mar 2020.