Efficacy of Early Administration of Liposomal Amphotericin B in Patients with Septic Shock: A Nationwide Observational Study

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Abstract

To determine the most suitable time to initiate liposomal amphotericin B (L-AMB) treatment in patients with invasive fungal infections**,** patients with septic shock treated with L-AMB were identified from the Japanese Diagnosis Procedure Combination national database to determine their survival rates following septic shock onset, mortality during shock, and shock cessation period. We identified 141 patients administered L-AMB: 60 patients received treatment on the day of septic shock onset (early L-AMB group), whereas 81 patients received treatment after the onset (delayed L-AMB group). Survival rates after septic shock onset were higher in the early L-AMB group than in the delayed L-AMB group (4 weeks: 68.4% vs 57.9%, *P*=0.197; 6 weeks: 62.2% vs 44.5%, *P*=0.061; 12 weeks: 43.4% vs 35.0%, *P*=0.168, respectively). Mortality during septic shock was significantly lower in the early L-AMB group than in the delayed L-AMB group (13% vs 42%, *P*<0.001), with a significant difference confirmed after adjusting for confounding factors (odds ratio: 0.240, 95% confidence interval: 0.096-0.601, *P*=0.002). Septic shock cessation period was shorter in the early L-AMB group than in the delayed L-AMB group (7.0±7.0 days vs 16.5±15.4 days, *P*<0.001). L-AMB administration at septic shock onset could be associated with early shock cessation and decreased mortality.

Introduction

Invasive fungal infections (IFIs) frequently occur in immunocompromised patients and critically-ill patients, and are associated with high rates of morbidity and mortality[1–6]. Identifying the appropriate time to start antifungal treatment especially for severe patients is thus crucial to improving the prognosis. For example, in candidemia, a significant reduction in crude mortality was observed if antifungal medication was initiated within 24 hours of the date of positive blood culture[7,8]. Furthermore, a trend toward reduced crude mortality has been reported with the initiation of antifungal medication within 48 or 72 hours of the onset of septic shock due to candidemia[9,10]. Conversely, prophylactic or empiric antifungal administration has been reported to reduce the incidence of IFIs but not improve crude mortality[11,12]. Additionally, in patients with septic shock caused by candidemia, the time from positive blood cultures to the start of antifungal medication did not differ between the survival and death groups[13]. As a result, the appropriate timing of treatment initiation for patients with severe IFI remains unclear.

Most clinical studies on the timing of antifungal drug initiation have been conducted in candidemia and only few studies on empirical treatments have been performed. However, because the positive rate of fungal cultures, including blood cultures, is not high enough[14], empirical treatment is often used in actual clinical practice. Therefore, knowledge of the appropriate time to initiate empirical treatment with antifungal drugs is needed.

Liposomal amphotericin B (L-AMB) has a broad anti-fungicidal spectrum that covers most clinically relevant yeasts and molds that cause mycosis, such as candidiasis, aspergillosis, cryptococcosis, and mucormycosis[15]. L-AMB is used as a first-line drug in critically-ill IFI patients with candidiasis,

aspergillosis, and mucormycosis, which exhibit resistance to other antifungal drugs[16]. Thus, we aimed to clarify the effect of L-AMB administration timing on the outcome of septic shock patients requiring IFI treatment.

Results

Comparison of baseline Characteristics

In total, 6,640 patients administered L-AMB were selected. Thereafter, we identified 141 patients administered L-AMB on the day of or after septic shock onset: 60 patients received early L-AMB treatment at septic shock onset (early L-AMB group) whereas 81 patients received delayed L-AMB treatment on and after the day following septic shock onset (delayed L-AMB group) (Fig. 1).

The characteristics of patients in both groups are shown in Table 1. The Charlson comorbidity index (CCI) and the proportion of immunosuppressed patients treated with corticosteroids or T cell immunosuppressants, patients with aspergillosis, and patients treated in the hematology department were higher in the early L-AMB group than the delayed L-AMB group. However, older patients, those requiring renal replacement therapy (RRT), and those treated in the surgical department were more frequent in the delayed L-AMB group than the early L-AMB group. In the delayed L-AMB group, L-AMB treatment was initiated at 5.6 ± 6.1 days from septic shock onset. In both groups, over 60% of patients switched to L-AMB from other antifungal drugs, the majority of which used echinocandins, such as micafungin and caspofungin, before L-AMB treatment initiation. The proportion of patients treated with voriconazole or itraconazole was higher in the early L-AMB group than the delayed L-AMB group (30% vs 15%, $P = 0.038$). This might be partly attributed to the higher presence of patients with aspergillosis in the early L-AMB group. In total, 35% patients initiated IFI treatment before septic shock onset (early L-AMB group 47% of subjects; delayed L-AMB group 26% of subjects; $P = 0.013$). For patients administered IFI treatment before septic shock onset, no significant difference in the duration from IFI treatment initiation to septic shock was found between those in the early (12.9 ± 12.7 days, N = 28) and delayed L-AMB groups (9.7 ± 16.3 days, N = 21, $P = 0.478$).

Table 1
Characteristics of septic shock patients administered early or delayed L-AMB treatment.

Patient characteristics	Overall (N = 141)	Early L-AMB (N = 60)	Delayed L-AMB (N = 81)	P-value
Age (years)	68.4 ± 13.5	65.3 ± 13.5	70.7 ± 13.0	0.020
Sex, male (%)	90 (64%)	37 (62%)	53 (65%)	0.724
Preexisting comorbid conditions				
CCI	3.7 ± 3.1	4.4 ± 3.3	3.2 ± 2.9	0.035
Malignant tumor (%)	75 (53%)	36 (60%)	39 (48%)	0.176
G-CSF treatment for neutropenia (%)	29 (21%)	16 (27%)	13 (16%)	0.143
Corticosteroid (≧ 0.3 mg/kg/day Prednisolone) (%)	62 (44%)	33 (55%)	29 (36%)	0.027
T cell immunosuppressants	35 (25%)	21 (35%)	14 (17%)	0.019
Diabetes mellitus with insulin treatment (%)	32 (23%)	12 (20%)	20 (25%)	0.548
Gastrointestinal surgery within 30 days (%)	12 (9%)	2 (3%)	10 (12%)	0.071
CV catheter (%)	100 (71%)	47 (78%)	53 (65%)	0.133
Interventions				
ICU admission (%)	39 (28%)	14 (23%)	25 (31%)	0.348
Renal replacement therapy (%)	43 (30%)	12 (20%)	31 (38%)	0.026
Mechanical ventilation (%)	56 (40%)	24 (40%)	32 (40%)	1.000
CV catheter replacement within the following day (%)	22 (16%)	11 (18%)	11 (14%)	0.487
L-AMB administration				
Average daily dosing (mg/kg)	2.9 ± 1.0	2.9 ± 1.0	2.9 ± 1.0	0.919
Duration (days)	15.7 ± 13.9	18.2 ± 16.6	13.8 ± 11.2	0.081
L-AMB administration initiation after the onset of septic shock (days)	3.2 ± 5.4	0.0 ± 0.0	5.6 ± 6.1	NA
Initiation of IFI therapy before the onset of septic shock[a]	49 (35%)	28 (47%)	21 (26%)	0.013
Antifungal drug treatment before the initiation of L-AMB therapy (%)[b]				

Patient characteristics	Overall (N = 141)	Early L-AMB (N = 60)	Delayed L-AMB (N = 81)	P-value
Overall	90 (64%)	39 (65%)	51 (63%)	0.860
Echinocandin (micafungin, caspofungin)	69 (49%)	27 (45%)	42 (52%)	0.496
Azole not for Aspergillosis (fluconazole)	17 (12%)	8 (13%)	9 (11%)	0.795
Azole for Aspergillosis (itraconazole, voriconazole)	30 (21%)	18 (30%)	12 (15%)	0.038
Treatment department (%)				
Hematology	46 (33%)	27 (45%)	19 (23%)	0.011
The internal department (except for hematology)	63 (45%)	26 (43%)	37 (46%)	0.864
The surgical department	27 (19%)	5 (8%)	22 (27%)	0.005
Others[c]	2 (1%)	0 (0%)	2 (2%)	0.508
Unknown	3 (2%)	2 (3%)	1 (1%)	0.575
Diagnosis (%)				
Aspergillosis	31 (22%)	19 (32%)	12 (15%)	0.023
Candidiasis	17 (12%)	9 (15%)	8 (10%)	0.436
Others[d]	29 (21%)	9 (15%)	20 (25%)	0.207
Unknown[e]	65 (46%)	24 (40%)	41 (51%)	0.235

Categorical variables are presented as frequencies and proportions (%) while continuous variables are expressed as mean ± standard deviation. Welch's t-test was employed to compare two groups for continuous variables, while the Fisher's exact test was used for two categorical variables.

CCI, Charlson comorbidity index; CV, central venous; G-CSF, granulocyte-colony stimulating factor; ICU, intensive care unit; L-AMB, liposomal-amphotericin B, NA; not analyzed.

[a]IFI treatment was defined as the time from initiation of intravenous injection treatment with antifungal drugs to discontinuation, which was defined as an administration interval ≥ 2 days. This period includes the date of L-AMB therapy initiation.

[b]Oral and injection antifungal drugs were evaluated.

[c]Other treatment department included anesthesiology and emergency medicine.

[d]Other diagnosis included cryptococcosis, zygomycosis, coccidioidomycosis, blastomycosis, maduramycosis, and unclassified or unspecified mycosis.

[e]Unknown diagnosis included patients without any mycosis diagnosis and those with neutropenia.

Comparison of survival rates after septic shock onset

Survival rates at 4 (68.4% vs 57.9%, *P* = 0.197), 6 (62.2% vs 44.5%, *P* = 0.061), and 12 (43.4% vs 35.0%, *P* = 0.168) weeks after septic shock onset were higher in the early L-AMB group than the delayed L-AMB group, albeit without statistical significance (Fig. 2). Sensitivity analysis revealed that survival rates did not significantly differ between patients whose L-AMB treatment was initiated within the day after septic shock onset and those whose treatment was initiated on and after two days following the onset; and patients whose L-AMB treatment was initiated within the two days after septic shock onset and those whose treatment was initiated on and after three days following the onset (Table S1).

Comparison of mortality during septic shock

Mortality during septic shock treatment was significantly lower in the early L-AMB group than the delayed L-AMB group (13% vs 42%, *P* < 0.001) (Table 2). Through univariate logistic regression analysis, five variables associated with mortality during septic shock (*P* < 0.2) (delayed L-AMB initiation, male, intensive care unit (ICU) admission, RRT, and treatment out of the hematology department) were identified (Table 3). By using these variables in multivariate regression analysis, we found that only early L-AMB initiation was negatively associated with mortality during septic shock (odds ratio [OR]: 0.240, 95% confidence interval [CI]: 0.096–0.601, *P* = 0.002) (Table 3). We also conducted a univariate logistic regression analysis with three variables that had a significant difference in Table 1 but were not included in Table 3 (i.e., azole treatment for Aspergillosis before the initiation of L-AMB treatment, treatment in the surgical department, and aspergillosis diagnosis; these variables might be related to mortality during septic shock (*P* < 0.2) (Table S2)). Thereafter, we performed a multivariate regression analysis with the model, including these variables and other variables presented in Table 3. We confirmed that early L-AMB initiation was negatively associated with mortality during septic shock (OR 0.246, 95% CI 0.097–0.625, *P* = 0.003) (Table S3). Sensitivity analysis demonstrated that mortality during septic shock was significantly lower in patients administered early L-AMB treatment within the day after septic shock onset or within two days after the onset than in patients administered late treatment (Table S4).

Table 2
Mortality during septic shock treatment in patients administered early or delayed L-AMB treatment.

	Overall (N = 141)	Early L-AMB (N = 60)	Delayed L-AMB (N = 81)	P-value
Numbers and mortality during septic shock treatment	42 (30%)	8 (13%)	34 (42%)	< 0.001

L-AMB, liposomal-amphotericin B.

Table 3
Logistic regression analysis of the factors associated with mortality during septic shock treatment.

	Univariate regression		Multivariate regression	
Variables	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Characteristics of antifungal drug use				
Timing of L-AMB treatment, Early (vs Delayed)	0.213 (0.090–0.505)	< 0.001	0.240 (0.096–0.601)	0.002
L-AMB average daily dosing, mg/kg/day	1.168 (0.820–1.662)	0.390		
Antifungal drug treatment before the initiation of L-AMB treatment, with (vs without)[a]	1.625 (0.744–3.550)	0.223		
Initiation of IFI therapy before the onset of septic shock, with (vs without)[b]	1.424 (0.675–3.003)	0.354		
Patient characteristics				
Age, ≥ 65 years (vs < 65 years)	1.074 (0.507–2.277)	0.852		
Sex, male (vs female)	2.702 (1.169–6.245)	0.020	2.421 (0.984–5.958)	0.054
CCI, score	1.002 (0.893–1.125)	0.971		
G-CSF treatment for neutropenia, with treatment (vs without treatment)	0.700 (0.274–1.791)	0.457		

CCI, Charlson comorbidity index; CI, confidence interval; CV, central venous; G-CSF, granulocyte-colony stimulating factor; ICU, intensive care unit, IFI, invasive fungal infection; L-AMB, liposomal-amphotericin B.

[a]Oral and injection antifungal drugs were evaluated.

[b]IFI treatment was defined as the time from initiation of intravenous injection treatment with antifungal drugs to discontinuation, which was defined as an administration interval ≥ 2 days. This period includes the date of L-AMB therapy initiation.

	Univariate regression		Multivariate regression	
Corticosteroid (≧ 0.3 mg/kg/day Prednisolone), with (vs without)	0.615 (0.292–1.294)	0.200		
T cell immunosuppressants, with (vs without)	0.766 (0.323–1.814)	0.544		
Other interventions/Treatment department of physicians				
ICU admission, with (vs without)	2.380 (1.094–5.178)	0.029	1.842 (0.763–4.443)	0.174
CV catheter replacement within the following day, with (vs without)	0.865 (0.313–2.389)	0.779		
Renal replacement therapy, with (vs without)	3.004 (1.399–6.451)	0.005	1.861 (0.796–4.353)	0.152
Hematology, with (vs without)	0.457 (0.197–1.061)	0.068	0.831 (0.322–2.145)	0.701

CCI, Charlson comorbidity index; CI, confidence interval; CV, central venous; G-CSF, granulocyte-colony stimulating factor; ICU, intensive care unit, IFI, invasive fungal infection; L-AMB, liposomal-amphotericin B.

[a]Oral and injection antifungal drugs were evaluated.

[b]IFI treatment was defined as the time from initiation of intravenous injection treatment with antifungal drugs to discontinuation, which was defined as an administration interval ≧ 2 days. This period includes the date of L-AMB therapy initiation.

Septic shock was ceased earlier in the early L-AMB group (7.0 ± 7.0 days, median: 4.5 days) than the delayed L-AMB group (16.5 ± 15.4 days, median: 12.0 days, $P < 0.001$) (Fig. 3).

Discussion

Herein, we observed an improvement in mortality during shock and early shock cessation in septic shock patients who started L-AMB treatment at septic shock onset. Importantly, patients analyzed in this study may include patients with various IFIs and those without IFIs. However, cases that were not tested for fungus were excluded, and patients without the possibility of IFI were not included. Several studies have revealed that early initiation of antifungal drug administration improves the outcome of patients with candidiasis[7,8]. Our findings demonstrate that the timing of L-AMB administration affects the prognosis of septic shock in a population with confirmed cases and empiric situations. The impact of such results on

clinical practice is significant as there are many situations where the diagnosis cannot be confirmed in clinical practice.

Because the backgrounds of patients in the early and delayed L-AMB groups differed markedly in this study, we carefully adjusted for confounding factors. For example, the proportion of patients treated in the hematology department was higher in the early L-AMB group, whereas the proportion of patients treated in the surgical department was higher in the delayed L-AMB group. We were mainly concerned that the difference in the overall management ability for IFIs between hematologists accustomed to treating IFIs and surgeons unfamiliar with IFIs may have influenced the difference in crude mortality between the two groups. Therefore, we evaluated the attribute (hematology), immunosuppression state (e.g., neutropenia treated with granulocyte-colony stimulating factor (G-CSF)), and risk factors of poor treatment outcome of candidiasis (e.g., central venous (CV) catheter replacement) in logistic regression analysis. Although we identified more variables (one additional variable) than the permissible number (4) after univariate regression screening, all factors were included in the multivariate regression model to adjust all important confounding factors. Collectively, we revealed the negative association between mortality during septic shock and early L-AMB initiation.

However, the difference in survival rates at four weeks after the onset of septic shock did not reach statistical significance between the groups. These results align with prior findings, such as the association between crude mortality at 30 days following positive blood culture and age, RRT, intubation, and primary source, but not prompt proper antifungal treatment[10]. The significant difference in mortality during septic shock may be due to differences in the causes of death. Most deaths during septic shock in this study may have been due to IFIs, which can be treated with L-AMB to improve prognosis. However, because the duration of septic shock was nine days (median) in all patients, septic shock might have already improved in many patients within four weeks after septic shock onset. Nonetheless, these patients may have died from primary diseases that were unaffected by L-AMB treatment as many patients who develop IFI have a serious background illness and often have a poor prognosis.

If early L-AMB administration improves the prognosis of IFI-induced septic shock, early administration of other antifungal drugs could also improve the prognosis. However, the history of antifungal drug administration before L-AMB initiation and IFI initiation before septic shock onset had no effect on mortality during septic shock. These results suggest that early L-AMB initiation may be particularly important.

Here, 64% of patients were switched from other antifungal drugs to L-AMB, suggesting that a switch to L-AMB is effective even for septic shock antifungal treatment. This switching might be partly attributed to insufficient treatment outcomes of other antifungal drugs. Echinocandin-resistant *Candida* has been reported[17]; echinocandins are not used as first-line drugs against invasive pulmonary aspergillosis and are ineffective for pulmonary mucormycosis[18]. Therefore, early L-AMB initiation might be beneficial, especially for septic shock patients whose target fungus has not been identified or patients infected with drug susceptibility-unconfirmed fungus.

Owing to data limitation, we opted to evaluate replacement instead of CV catheter removal, despite our inability to distinguish the re-detention in other blood vessels and the same blood vessel using guidewires. Furthermore, CV catheter replacement was not associated with reduced mortality during septic shock. This may be because IFI patients that opted to remove the catheter without inserting a new catheter were excluded or those with mycosis, except for candidiasis, were included.

Herein, clinicians in the hematology department, but not the surgical department, may initiate L-AMB administration at septic shock onset, suggesting that sufficient experience with L-AMB treatment is required for prompt treatment initiation. Both hematologists and physicians who are familiar with the use of L-AMB are infectious disease specialists. In cases of septic shock with possible IFI, an infectious disease physician's intervention on the day of onset may improve prognosis.

Because an administrative database was used, this study had several limitations. First, several confounding factors were not evaluated as data including source control (CV catheter removal etc.) and acute physiology and chronic health evaluation (APACHE) II, an indicator of infectious severity, could not be obtained. Alternatively, we opted to employ CV catheter replacement, ICU admission, RRT, and detailed patient characteristics as explanatory variables to validate the reliability of our results. Second, owing to the retrospective nature of this analysis, prospective studies are required to verify the results. A retrospective analysis might be suitable for evaluating the efficacy of early L-AMB initiation in septic shock patients owing to the difficulty involved in conducting a prospective study. Finally, because a comparative study with non-L-AMB treatment cases was not carried out, the characteristics of septic shock cases that should be treated with L-AMB were not captured. Further studies are needed to further identify patients requiring L-AMB treatment.

Methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki. The data herein were anonymously processed by the database provider (Medical Data Vision Co., Ltd) in accordance with the Act on the Protection of Personal Information of Japan and other related regulations. For the usage of unlinkable de-identified data, ethical approval and informed consent were waived according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare of Japan. The study received ethical approval from Nagasaki University School of Medicine Research Ethics Committee (approval number 18033038-5). This committee has waived the need for consent to conduct the study.

Study design and data source

This retrospective study was conducted with administrative claims data obtained from an electronic medical information database (Medical Data Vision Co., Ltd), which contains diagnosis procedure

combination (DPC) hospital data and medical fee reimbursement claims from 345 facilities in Japan. Baseline patient information included age, sex, diagnosis, and comorbidities at admission, coded using the International Classification of Diseases, 10th Revision (ICD-10) codes. The database also contained all drug dosages and administration dates during hospitalization. All interventional procedures were decoded from the original Japanese codes. DPC is an administrative database containing inpatient information. Therefore, patient follow-up began on admission day and ended on discharge date, transferal to other hospitals, or death.

Patient selection

We identified patients administered L-AMB during hospitalization between April 2008 and January 2018. Patients with septic shock were defined as subjects treated with catecholamines. Septic shock onset was defined as the date of catecholamine treatment initiation. Patients that began L-AMB treatment on the day of or after septic shock onset and those administered carbapenems at septic shock onset were selected to avoid the effects that arise as confounders owing to antibiotics. Patients who met the following criteria were excluded: 1) < 18 years old; 2) L-AMB daily dosing > 6 mg/kg body weight; 3) < 5 days of L-AMB treatment duration; 4) L-AMB administration before septic shock onset; 5) began L-AMB treatment after four weeks following septic shock onset; 6) no fungal infection tests such as culture, drug susceptibility tests of fungus, β-D-glucan, or antigens of *Aspergillus*, *Candida*, and *Cryptococcus* within seven days before the initiation of L-AMB administration; and 7) lacking required data, including body weight and outcome. The early L-AMB group included patients who initiated L-AMB treatment at septic shock onset, whereas the delayed group included patients who began treatment on and after the day following septic shock onset.

Variables and endpoints

We evaluated patient characteristics, including age, sex, IFI disease name, and antifungal drugs administered before L-AMB treatment initiation. Comorbidities were evaluated using CCI[19]. CCI has been widely used by researchers to measure case mix and burden of disease. It includes 17 conditions that have a major impact on survival and are defined by the ICD-10 codes[20]. A higher CCI depicts the presence of severe comorbidities. The presence of malignant tumor, neutropenia treated with G-CSF, corticosteroid treatment (≥ 0.3 mg/kg/day prednisolone conversion), diabetes treated with insulin, and T cell immunosuppressant therapy were assessed to evaluate the state of immunosuppression before and at septic shock onset. T cell immunosuppressant therapy was defined as treatment with calcineurins, anti-tumor necrosis factor α (TNFα) inhibitors, anti-lymphocyte monoclonal antibodies, and purine and pyrimidine analogs the day of or within the 90 days before septic shock onset[21]. The presence of a CV catheter insertion and a history of gastrointestinal surgery were retrieved to evaluate the risk factors associated with the outcome of IFI treatment. Digestive tract surgery was defined as a surgery that incised the esophagus, stomach, duodenum, jejunum, ileum, cecum, appendix, colon, and rectum the day of or within 30 days before septic shock onset. The presence of interventions, including ICU admission, RRT, mechanical ventilation, and CV catheter replacement, was assessed to evaluate the state of patients

before and at septic shock onset. However, CV catheter removal was not evaluated as this was not included in the claims data. Initiation of IFI therapy before the onset of septic shock as well as oral and injection antifungal drug treatment before the initiation of L-AMB therapy were assessed to evaluate previous experience with antifungal treatment. IFI treatment was defined as the time from initiation of intravenous injection treatment with antifungal drugs to discontinuation, which was defined as an administration interval ≥ 2 days. This period includes the date of L-AMB therapy initiation. The attributes of clinicians were assessed to evaluate their experience with L-AMB dispensing or their capability to carry out patient management. Treatment departments were classified into 4 categories: hematology, which included clinicians with extensive experience in treating invasive pulmonary aspergillosis and pulmonary mucormycosis with L-AMB; internal departments, except the hematology department; surgical department; and other departments (e.g., emergency medicine). L-AMB or catecholamine treatment duration was defined as the time from treatment initiation to discontinuation. Treatment discontinuation was defined as an administration interval ≥ 8 or ≥ 2 days, respectively. Septic shock cessation was defined as catecholamine treatment termination. The following endpoints were assessed: 1) survival rates at 4, 6, and 12 weeks after septic shock onset, 2) mortality during septic shock treatment, and 3) duration until septic shock cessation.

Statistical analysis

The survival rate after septic shock onset was calculated using the Kaplan-Meier method and statistically evaluated with the log-rank test. Crude mortality during septic shock treatment was statistically evaluated with the Fisher's exact test. Logistic regression analyses were conducted to identify the factors associated with mortality during septic shock treatment. We selected 14 variables related to mortality in patients with septic shock from a clinical perspective. These variables included those related to antifungal treatment (timing of L-AMB treatment initiation, daily average dosing of L-AMB, history of antifungal drug administration before the initiation of L-AMB administration, initiation of IFI therapy before septic shock onset), patient characteristics (age, sex, CCI, presence of neutropenia with G-CSF administration, treatment with corticosteroid and T cell immunosuppressants), interventions (ICU admission, CV catheter replacement, and RRT), and clinician's attribute (hematology department). The variables were subjected to univariate binomial logistic regression analysis. Variables with a P value < 0.2 were subjected to multivariate logistic regression, and their OR and 95% CI were calculated. Regression analysis was also conducted after variables that significantly differed between the early L-AMB group and delayed L-AMB group in patient characteristics were included. Continuous variables are presented as average ± standard deviation. Welch's t-test was employed to compare two groups for continuous variables, while the Fisher's exact test was used for two categorical variables.

Declarations

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Author contributions

Study conception and design: M.T. Data analysis: A.T. Interpretation of data: all authors. Manuscript drafting: M.T. and A.T. Study supervision: all authors. Final approval for submission: all authors.

Competing Interests

K.I. received honorarium and research grant from Sumitomo Dainippon Pharma Co., Ltd. T.W. is a full-time employee of Sumitomo Dainippon Pharma Co., Ltd. A.T. and K.S. are full-time employees of Deloitte Tohmatsu Consulting LLC. Deloitte Tohmatsu Consulting LLC receives consulting fees from Sumitomo Dainippon Pharma Co., Ltd. All other authors have no conflict of interest.

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Figures

Figure 1.

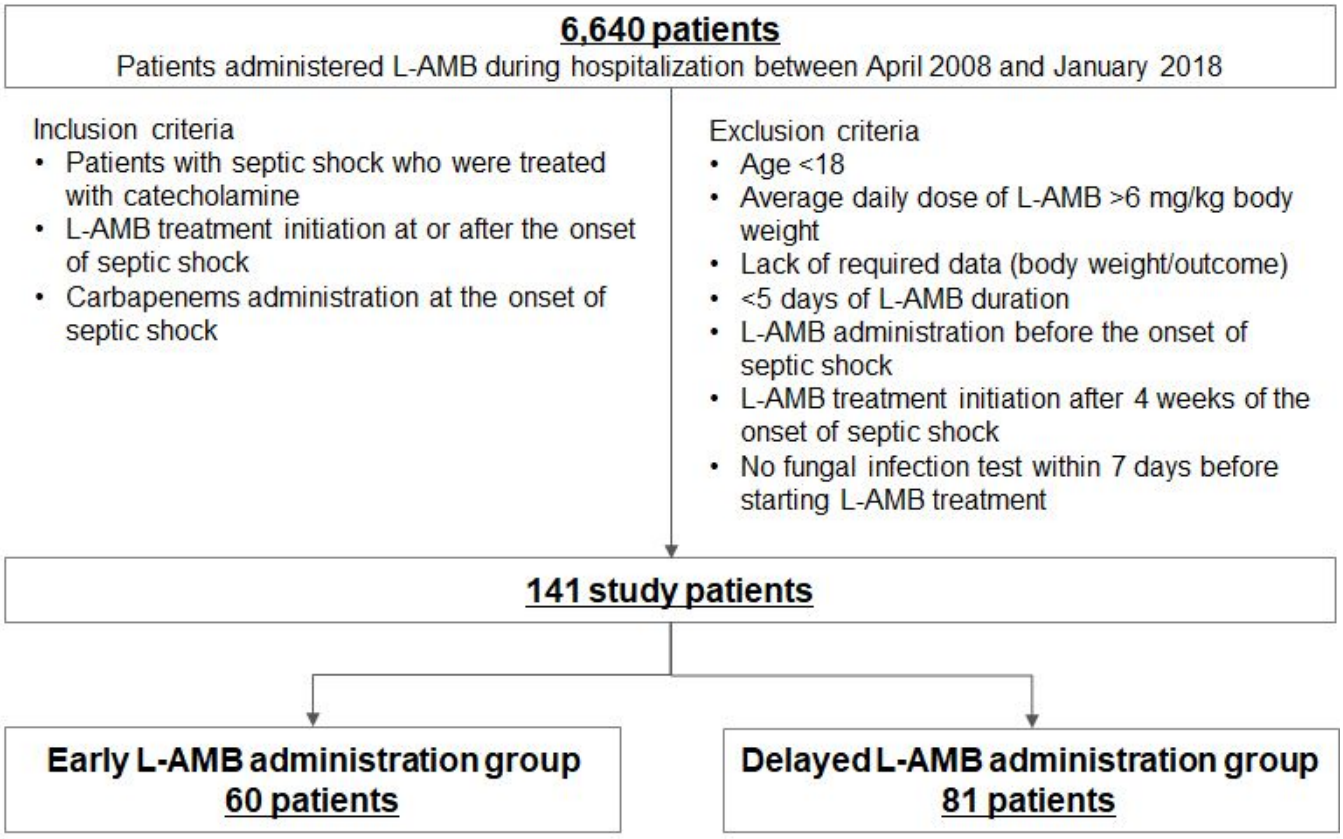

Figure 1

Flow chart for patient selection. L-AMB, liposomal-amphotericin B.

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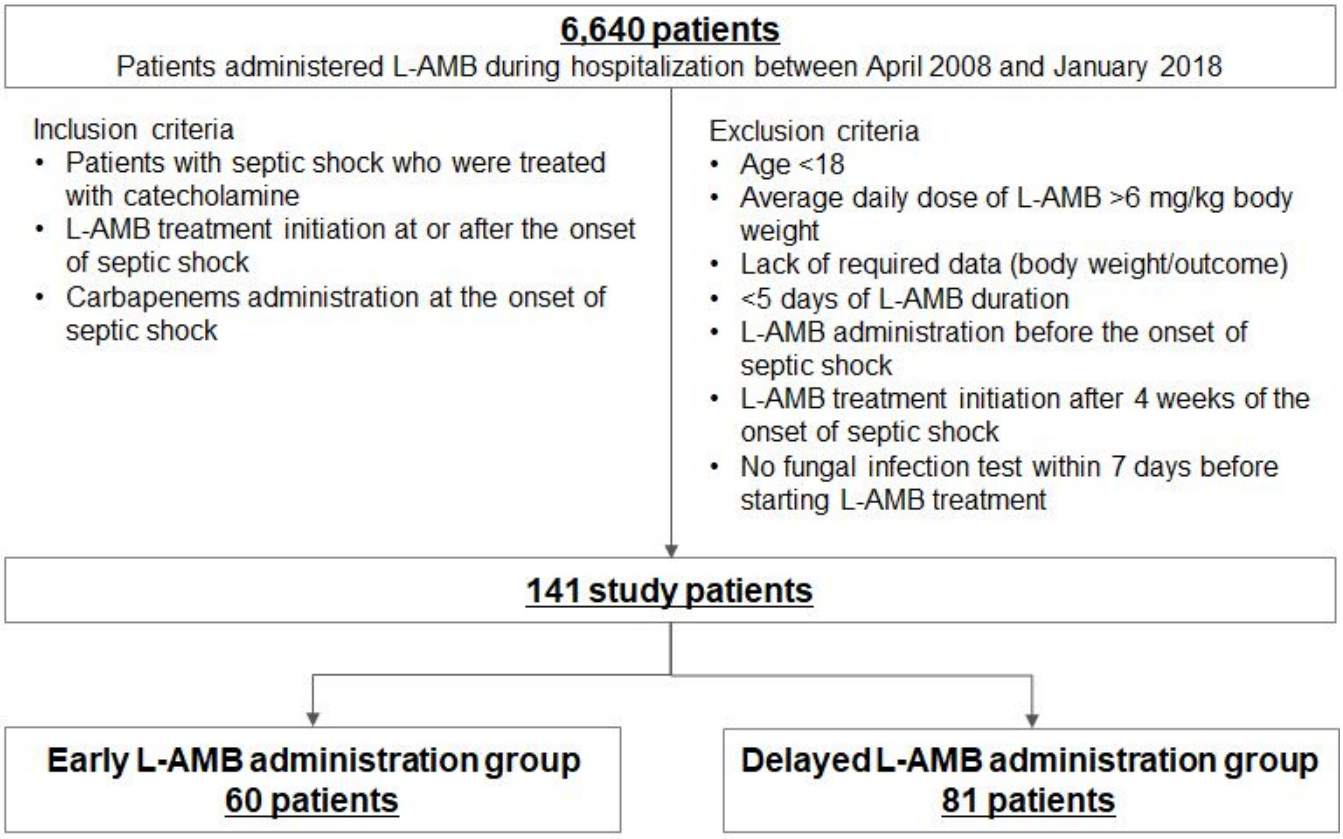

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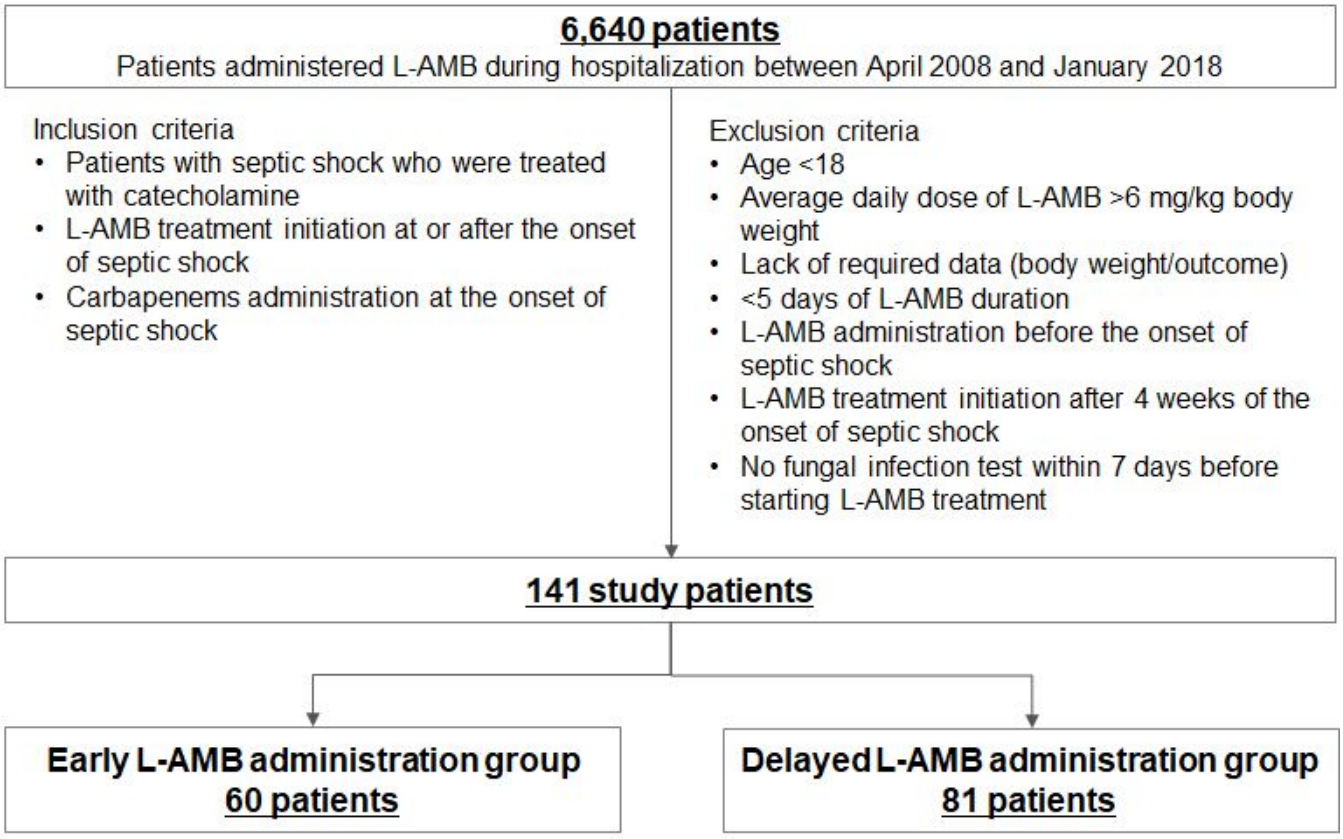

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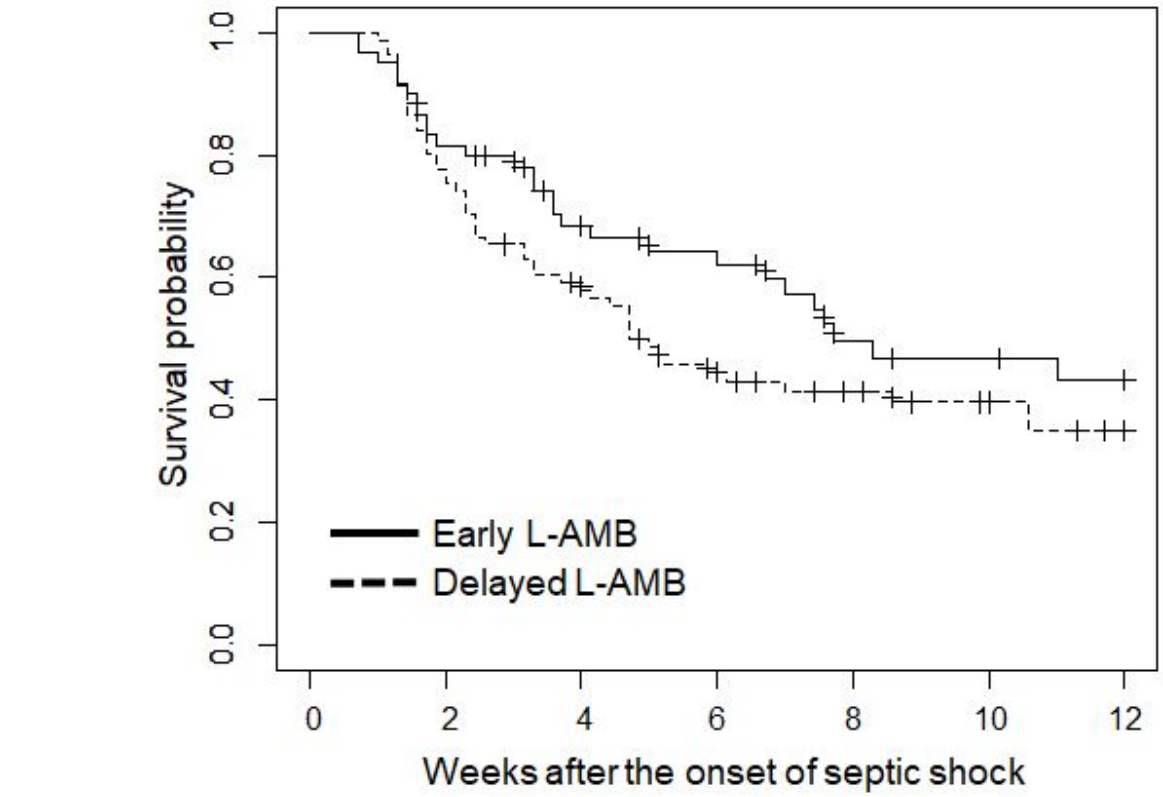

Number of patients at risk

Early L-AMB	60	48	35	30	17	15	13
Delayed L-AMB	81	63	46	31	24	18	13

Figure 2

Kaplan-Meier survival curve for septic shock patients administered early or delayed L-AMB treatment. L-AMB, liposomal-amphotericin B.

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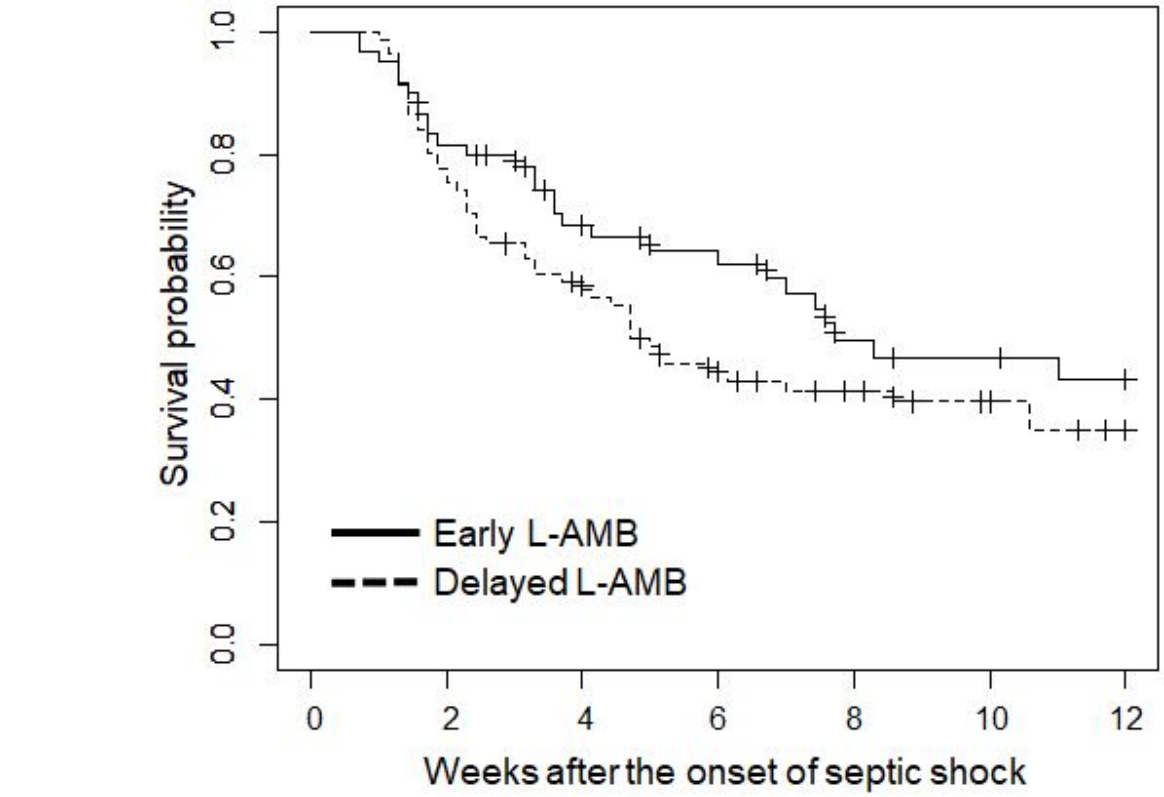

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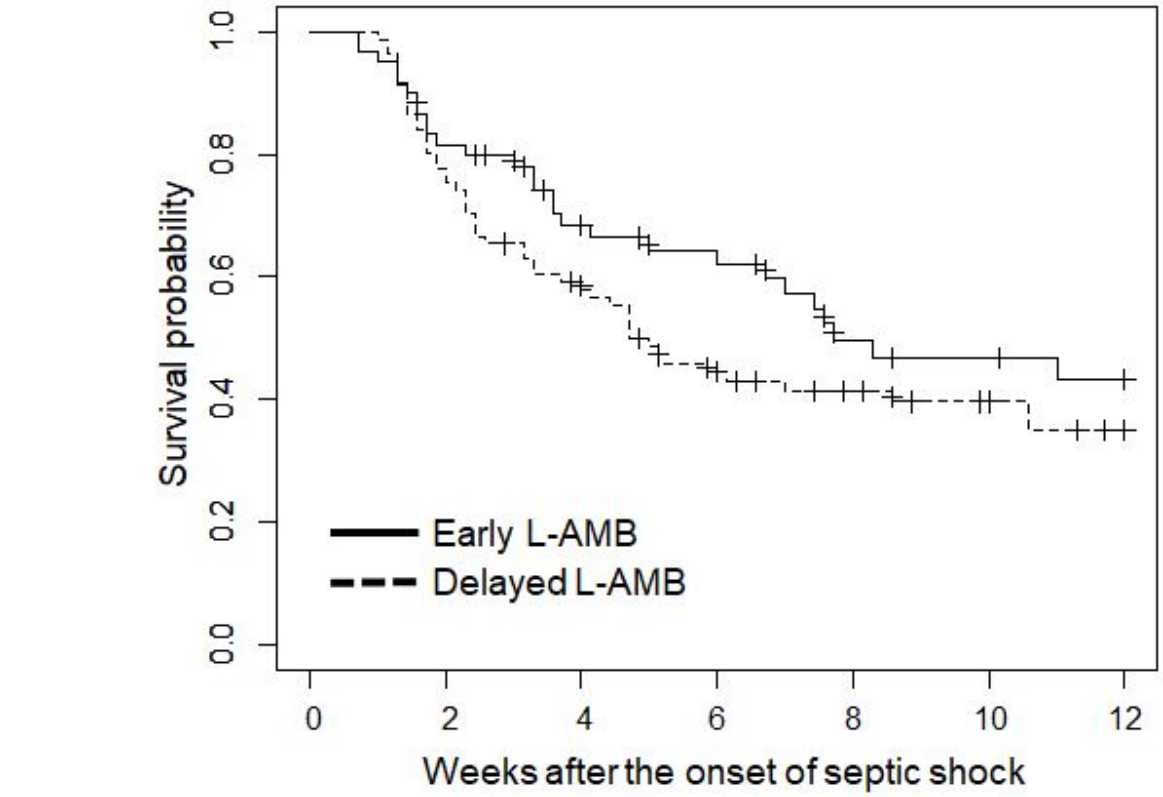

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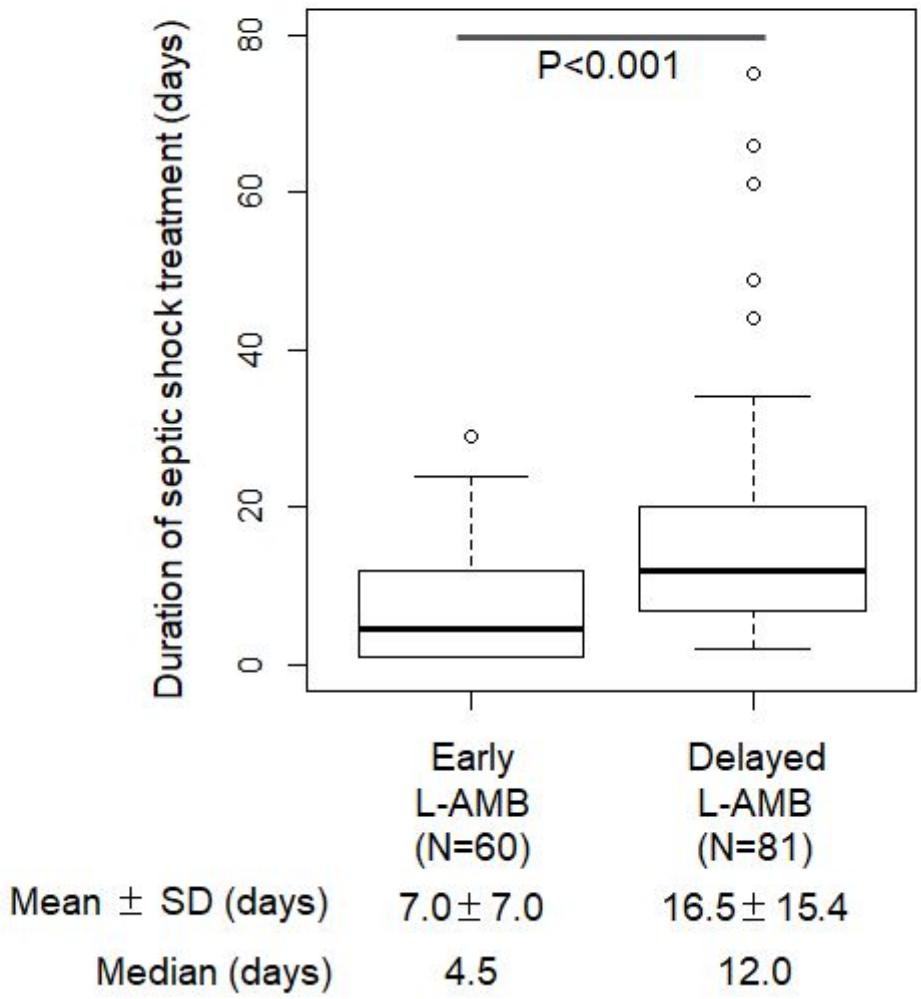

Figure 3

Duration of septic shock treatment for patients administered an early or delayed treatment of L-AMB. Welch's t-test was employed to compare two groups. L-AMB, liposomal-amphotericin B; SD, standard deviation.

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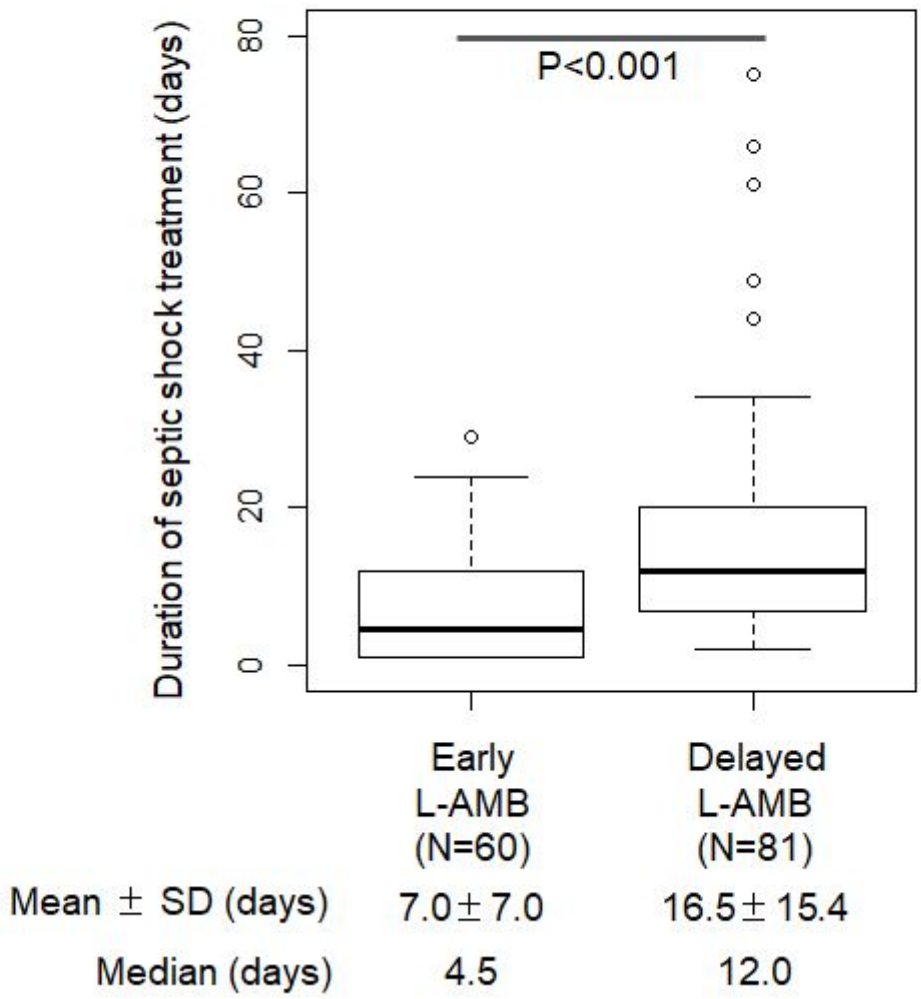

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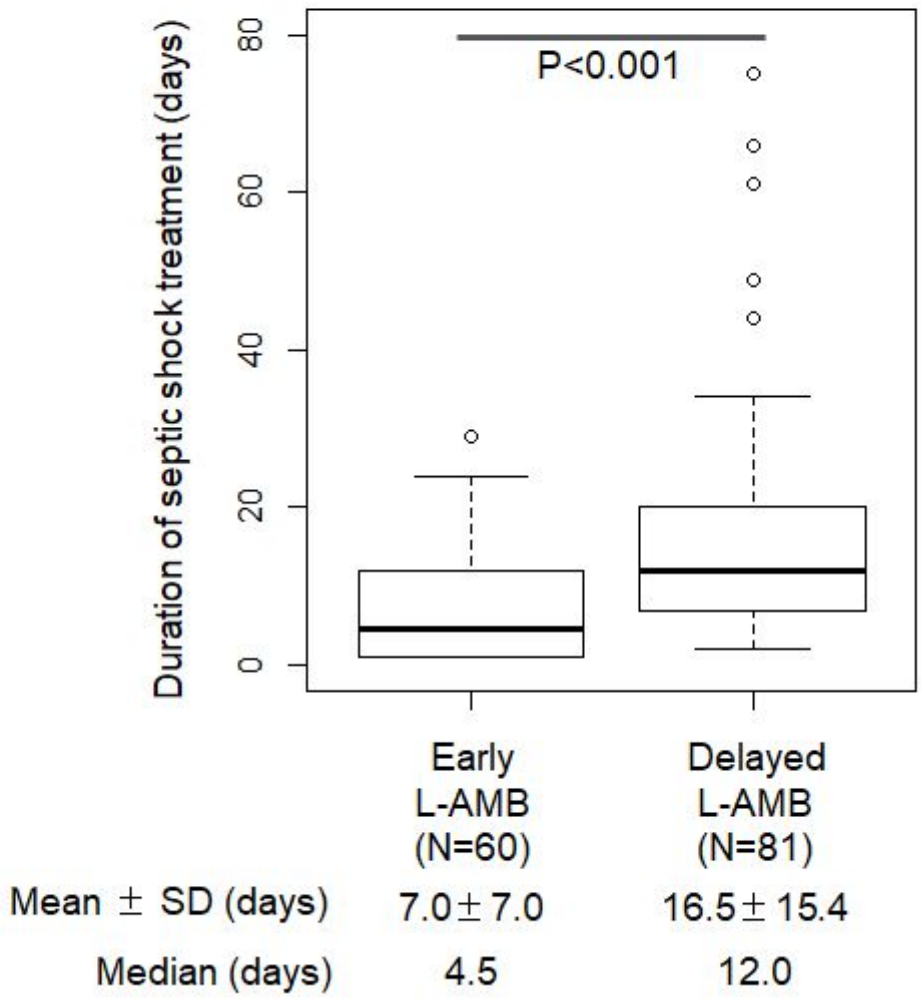

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Supplementary Files

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