

Original Article

Association of Weekend Admission and In-Hospital Mortality in Adult Patients with Acute Myeloid Leukemia in Japan

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The effect of weekend admission on patient mortality has been investigated in several therapeutic areas, including acute myeloid leukemia (AML), but the investigations' results are controversial. We evaluated the relationship between in-hospital mortality and weekend admission in adult patients with AML in Japan by conducting a retrospective observational study using administrative data from 144 acute care hospitals from which patients were discharged between April 2014 and March 2019. The primary endpoint was in-hospital mortality, compared between weekend and weekday admissions. Among the 1,340 eligible patients, 11% (150) were admitted during a weekend. The in-hospital mortality rates of the patients admitted during weekends and those admitted on a weekday were 28% (42/150) and 17% (204/1190), respectively. After an adjustment for covariates, weekend admission was associated with a significantly higher risk of in-hospital mortality than weekday admission (HR 1.70, 95%CI: 1.20-2.40; $p=0.003$). However, such an association was not observed in patients treated in a bio-clean room (HR 1.26, 95%CI: 0.65-2.42). Our results demonstrate that for patients with AML, weekend admission was independently associated with a higher risk of death during hospitalization. An appropriate system is necessary for these patients.

Key words: acute leukemia, weekend admission, in-hospital mortality, bio-clean room

The "weekend effect" has been investigated in healthcare settings worldwide, and controversial results have been obtained. Several research groups reported that patients with cardiac, neurologic, respiratory neonatal, or cancer emergencies who were admitted to a hospital during the weekend had a higher rate of in-hospital mortality compared to patients admitted on weekdays [1-7]. These reports suggested that hospitals provide routine care on weekdays but on weekends the care that is provided is more limited or may even involve only emergency/urgent care. Poor outcomes were explained by reduced staffing and the nonavailability of examinations [8,9]. However, no

significant effect of weekend versus weekday admission on in-hospital mortality was observed in patients with stroke, severe acute pancreatitis, or urgent laparoscopic cholecystectomy for acute cholecystitis in Japan [10-12].

A single-center study conducted at the Cleveland Clinic (Ohio, USA) concerning patients with acute myeloid leukemia (AML) indicated that weekend admission did not affect patient survival; however, the Clinic's hospital staffing and diagnostic and procedural services were completely functional during weekends [13]. Another investigation showed that weekend admission increased the mortality rate of patients with acute leukemia [14]. Japan's healthcare system differs

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from those of the countries where these studies were conducted, and we thus speculated that weekend admission for AML symptoms may have different outcomes in Japan. We conducted the present study to compare the in-hospital mortality rate between patients with AML admitted on weekends and those admitted on weekdays in Japan.

Materials and Methods

Data sources. We performed a retrospective observational study using in-hospital administrative data collected by Japan's Diagnosis Procedure Combination (DPC) payment scheme. The DPC system, which has been implemented in Japan since 2003, is a case-mix classification used for reimbursement in the Per-Diem Payment System for patients with acute-phase hospitalization. The DPC data contain patient information such as the most resource-consuming disease, comorbidities at admission, discharge status, and treatment procedures. The patients' diagnoses were classified based on the International Classification of Diseases, 10th revision (ICD-10) codes. The DPC data also provide clinical information regarding the use of medical resources, including admission to a bio-clean room, clinical examinations, and surgical procedures.

This study was approved by the Ethics Committees of Yokohama City Minato Red Cross Hospital (unique identifier: 2017-19) and Chiba University (unique identifier: 3309).

Study population. The data analyzed for the study were gathered from hospitals participating in the DPC system. To select the study population, we identified the cases of the patients for whom AML was the most resource-consuming diagnosed disease by using the ICD-10 codes C920, C924, C925, C930, C940, C942 and who were discharged between April 1, 2014, and March 31, 2019. The additional criteria were: (1) age ≥ 40 and < 80 years; (2) hospitalization at an emergency department (*i.e.*, unplanned hospitalization); and (3) no prior history of hospitalization for AML. When a patient had been hospitalized more than once, only their first records were included in the analyses, in order to limit our analyses to initial hospitalizations. We stratified the eligible patients by day of admission into weekday and weekend groups.

Weekend admission. We defined weekdays as Monday through Friday and weekends as Saturday,

Sunday, Japanese statutory holidays, and New Year week (from December 29 to January 3).

Outcome. The study's primary outcome was the all-cause in-hospital mortality rate in the groups of weekend and weekday admissions.

Statistical analyses. The patients' characteristics were compared between those with weekend and weekday hospital admissions. Continuous variables are expressed as the mean and standard deviation. The differences between weekend and weekday admissions were assessed using Wilcoxon's rank sum test. Categorical variables were compared using the χ^2 -test or Fisher's exact test. As patient characteristics, we included age, sex, admission by ambulance or referral, diagnosis, and comorbidities at admission (*e.g.*, disseminated intravascular coagulation [DIC], sepsis, and stroke). Teaching hospitals were defined as specialized training facilities certified by the Japanese Society of Hematology. Specialized training facilities are required to have ≥ 20 beds for hematology, operate specialized outpatient services, and employ at least one supervisory physician. In terms of treatment, admission to a hospital's bio-clean room was identified by the revenue code in the DPC system's medical fee table.

We calculated the unadjusted in-hospital mortality rates. The Kaplan-Meier survival curve was constructed, and the difference between weekend and weekday admissions was assessed with the log-rank test. For a multivariate analysis, we applied a Cox regression model using the patient characteristics and admission to a teaching hospital as adjustment variables. We also performed sub-group analyses based on admission to a bio-clean room during hospitalization in order to assess the effect of bio-clean room admission during hospitalization because hospitals can receive a premium fee for a bio-clean room. A *p*-value < 0.05 was considered significant.

Results

Study patients. A total of 1,340 patients with AML from 144 hospitals in Japan met all of the inclusion and exclusion criteria. Of these, 150 (11%) were admitted during a weekend, and 1,190 (89%) were admitted on a weekday.

Table 1 summarizes the patients' characteristics. More than 80% of the patients had been diagnosed with acute myeloblastic leukemia, and approx. 10% of the

patients had been diagnosed with acute promyelocytic leukemia. The patients who had been admitted on weekends were more frequently admitted via an ambulance compared to those admitted on a weekday. There were no significant between-group differences in sex, age, or comorbidities at admission such as DIC and sepsis, but significant difference in stroke.

In-hospital mortality. The in-hospital mortality rate of the patients admitted to the hospital during a weekend was 28% (42/150), and that of the patients admitted on a weekday was significantly lower at 17% (204/1,190) ($p=0.001$). Figure 1 depicts the in-hospital mortality according to the day of the week. Sunday admissions showed the highest mortality, and among

Table 1 Patients characteristics by weekday and weekend admissions

	Weekday n = 1,190	Weekend n = 150	P-value
Sex: Male	62.4%	55.3%	0.096
Age, years (Mean $\pm$ SD)	64.4 $\pm$ 10.8	62.5 $\pm$ 12.2	0.171
40–49	14.1%	22.0%	
50–59	16.2%	14.7%	
60–69	30.3%	26.0%	
70–79	39.4%	37.3%	
Diagnosis (ICD10)			0.636
Acute myeloblastic leukemia (C920)	84.7%	81.3%	
Acute promyelocytic leukemia (C924)	11.4%	14.7%	
Acute myelomonocytic leukemia (C925)	2.0%	3.3%	
Acute monoblastic leukemia (C930)	1.2%	0.7%	
Acute erythroid leukemia (C940)	0.4%	–	
Acute megakaryoblast leukemia (C942)	0.3%	–	
Admission by ambulance	14.1%	36.0%	<0.0001
Admission by referral	82.3%	72.7%	0.005
Comorbidities at admission			
DIC	16.1%	20.0%	0.230
Sepsis	9.6%	11.3%	0.496
Stroke	0.7%	2.7%	0.036
Admission of teaching hospital	48.7%	54.0%	0.217

DIC, disseminated intravascular coagulation.

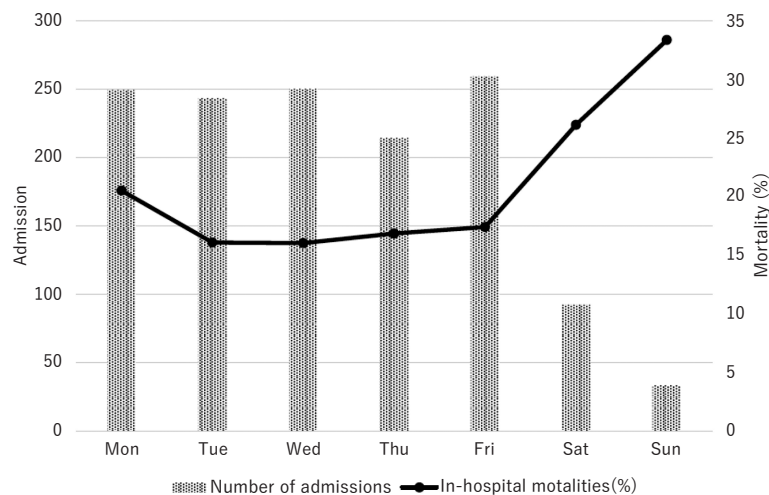


Fig. 1 The numbers of admissions and the in-hospital mortality rates for the weekend (n = 150 patients) and weekday (n = 1,190) admission groups.

the weekdays Monday tended to show a higher mortality rate. Of these in-hospital deaths, 17% (7/42) of the weekend-admission deaths and 5% (11/204) of the weekday-admission deaths occurred within 24 h after admission.

As shown by the Kaplan-Meier curve (Fig. 2), weekend admission was associated with a significantly higher risk of in-hospital mortality compared to weekday admission ($p=0.0008$). After the adjustment for the patients' baseline characteristics and admission to a teaching hospital, the adjusted hazard ratio (HR) for in-hospital death in the weekend-admission group was 1.70 (95% confidence interval [CI]: 1.20-2.40, $p=0.003$).

The in-hospital mortality rates of the patients who were or were not admitted to a bio-clean room during

hospitalization are presented in Table 2. Admission to a bio-clean room occurred in 84 of the 150 patients (56%) admitted on weekends and in 796 of the 1,190 patients (67%) admitted on weekdays ($p=0.008$). As suggested by the results of the multivariate Cox model, weekend admission to a bio-clean room was not associated with higher in-hospital mortality (adjusted HR 1.26, 95%CI: 0.65-2.42), but a corresponding significant association was observed in the patients who were not admitted to a bio-clean room (adjusted HR 1.62, 95%CI: 1.06-2.48).

Discussion

The results of our analyses demonstrated that the in-hospital mortality rate of patients with AML was

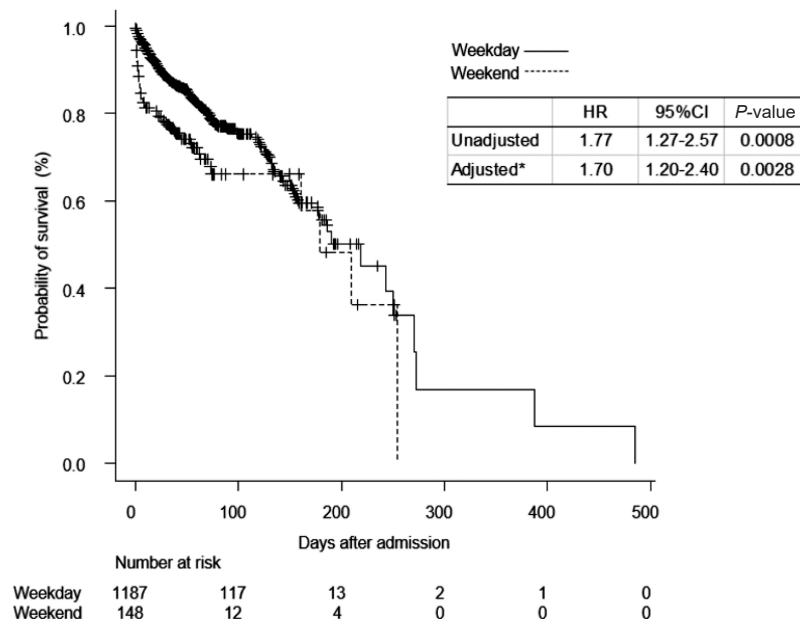


Fig. 2 The Kaplan-Meier curve and hazard ratios for the weekend effect.

*Adjusted for sex, age, diagnosis, ambulance use, referral, disseminated intravascular coagulation (DIC), sepsis, stroke, and admission to a teaching hospital.

Table 2 Subgroup analysis by admission to a bio-clean room during hospitalization

Bio-clean room	In hospital mortality (no. of deaths/no. of patients)		Adjusted HR for death (95% CI)	P-value
	Weekday	Weekend		
Yes	10.6% (84/796)	13.1% (11/84)	1.26 (0.65-2.42)	0.490
No	30.5% (120/394)	47.0% (31/66)	1.62 (1.06-2.48)	0.026

Adjusted for sex, age, diagnosis, ambulance, referral, DIC, sepsis, stroke and admission of teaching hospital.

significantly higher when the patients were admitted to the hospital during a weekend compared to when they were admitted on a weekday. To the best of our knowledge, this is the first study to demonstrate the weekend effects of admission for AML in Japan. We also observed that the AML patients who were not treated in a bio-clean room showed the weekend effect, whereas no such effect was observed in the patients who were treated in a bio-clean room.

We suspect that the reason for this discrepancy in mortality rates between patients admitted on weekends and weekdays is based on early death (*i.e.*, death within a few days after admission), as shown by the Kaplan-Meier curve. Moreover, the in-hospital mortality rate within 24 h after admission in the patients admitted on weekends was approximately threefold higher than that in the patients admitted on weekdays. We speculate that the patients admitted on weekends had more severe conditions due to a delayed diagnosis compared to the patients admitted on weekdays. Because of the nature of the DPC system's administrative claims, the primary departments at the patients' admissions in this study were not known, but if the patients admitted during weekends were initially treated by non-hematologists, their diagnosis and treatment initiation may have been delayed and consequently, early death occurred for those patients because of difficulties in disease management. The disease management at the early phase of AML patients' admission is critical to save these patients. Our findings indicate that patients with possible AML should be admitted to the appropriate hospital immediately, regardless of whether it is a weekend or weekday.

The evidence from other studies regarding weekend admissions for patients with AML is inconsistent. The Cleveland Clinic study mentioned in the Introduction indicated an absence of weekend effects on patients with AML, which is likely to have been observed because of the full staffing and all-day examination systems available at that clinic, even on weekends [13]. However, another retrospective cohort study showed that patients with acute leukemia who were admitted during a weekend had significantly increased mortality compared to those admitted on weekdays, except at teaching hospitals [14]. In that study, Parikh *et al.* observed that (*i*) patients with weekend admissions were less likely to undergo a bone marrow biopsy compared to those with weekday admissions, and (*ii*) the performance of a bone marrow biopsy independently predicted lower in-

hospital mortality in a multivariable hierarchical mixed-effect model [14]. We suspect that a definitive diagnosis based on a bone marrow examination that is delayed due to insufficient staff resources on weekends may have failed to result in immediate chemotherapy.

Two reasons can be considered to explain our present findings. First, 71 (49%) of the hospitals in the present study did not admit patients with AML on weekends. These hospitals would not have fully maintained service functions to treat patients with AML during weekends, and consequently, patients would be transferred to tertiary-care hospitals. Moreover, patients without a referral may not have been admitted to the appropriate hospital for the treatment of AML. Such situations are likely to affect patient outcomes, as patients cannot be treated at the nearest hospitals and the proper diagnosis and treatment may be delayed during the transfer process, especially for patients admitted after arriving by ambulance.

Second, admission to a bio-clean room occurred less frequently among the present patients admitted during a weekend. This may be due to a lack of available beds, the absence of management-level staff during weekend, and/or a lack of indications for treatment in a bio-clean room due to too-serious conditions of patients admitted during a weekend. The treatment settings for such critically ill patients are important. The staff of bio-clean rooms have experience providing specialized care for patients with serious hematologic disease, which would influence patients' outcomes. Ensminger *et al.* reported that the mortality rates of patients admitted to an ICU did not differ between those with weekend and weekday admissions [15], and the same result was obtained in our present study. The efficacy of admission to a bio-clean room for the treatment of leukemia has been demonstrated since 1970 [16]. According to a study by the U.S. National Institutes of Health, the results of the treatment of leukemia with antibiotics are remarkable when this treatment is performed in biologically clean and aseptic conditions that can help extend the patient's life [16].

The present study has several limitations. First, the DPC data records diagnoses using ICD-10 coding that may not reflect clinical conditions (as opposed to the clinical conditions in planned prospective studies). Second, our analyses did not include more detailed clinical information such as the severity of the patients' illness, their medical history, laboratory findings, or

the length of time from admission to the confirmed diagnosis of AML, due to the analyses' dependence on administrative DPC data. Moreover, the mortality data were available from the DPC, but the causes of death were not known. Third, the study population was comprised of only Japanese patients, and our findings may not apply to patients in other countries. This study is apparently the first to investigate the weekend effect on patients with AML in Japan, but given these study limitations, further research is necessary.

In conclusion, our analyses revealed that weekend admission for patients with AML in Japan was associated with a significantly higher in-hospital mortality rate than weekday admission. In addition, the in-hospital mortality rate was reduced in the patients who were admitted to a bio-clean room.

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