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Original Article

Impact of Intensive Care Unit-Acquired Infection on Hospital Mortality in Japan: A Multicenter Cohort Study

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Abstract:

Objectives: To elucidate factors associated with hospital mortality in intensive care unit (ICU) patients and to evaluate the impact of ICU-acquired infection on hospital mortality in the context of the drug resistance of pathogens.

Methods: By using the Japanese Nosocomial Infection Surveillance (JANIS) database, 7,374 patients who were admitted to the 34 participating ICUs between July 2000 and May 2002, were aged 16 years or older, and who stayed in the ICU for 48 to 1,000 hours, did not transfer to another ICU, and did not become infected within 2 days after ICU admission, were followed up until hospital discharge or to Day 180 after ICU discharge. Adjusted hazard ratios (HRs) with the 95% confidence intervals (CIs) for hospital mortality were calculated using Cox's proportional hazard model.

Results: After adjusting for sex, age, and severity-of-illness (APACHE II score), a significantly higher HR for hospital mortality was found in ventilator use, central venous catheter use, and ICU-acquired drug-resistant infection, with a significantly lower HR in elective or urgent operations and urinary catheter use. The impact of ICU-acquired infection on hospital mortality was different between drug-susceptible pathogens (HR 1.11, 95% CI: 0.94-1.31) and drug-resistant pathogens (HR 1.42, 95% CI: 1.15-1.77).

Conclusions: The use of a ventilator or a central venous catheter, and ICU-acquired drug-resistant infection were associated with a high risk of hospital mortality in ICU patients. The potential impact on hospital mortality emphasizes the importance of preventive measures against ICU-acquired infections, especially those caused by drug-resistant pathogens.

Key words: multicenter cohort study, hospital mortality, ICU, nosocomial infection, drug resistance

Introduction

The intensive care unit (ICU) is known to be a hot spot of infections (1,2). The 1-day point-prevalence study of 1,417 ICUs in 17 Western European countries, so called the EPIC study, showed that the prevalence rate of infection in ICUs was 44.8%, and almost half of the infections were acquired in the ICU (20.6%) (3).

ICU-acquired infection is recognized as one of the most important determinants for the outcome of ICU patients. However, the precise relationship in terms of cause and effect between ICU-acquired infection and hospital mortality has yet to be defined. There have been few cohort studies in which ICU patients were followed up until hospital discharge. A cohort study of 28 ICUs in 8 countries showed that the hospital mortality rate in patients with ICU-acquired infection was 32.1%, against 12.1% of that in non-infected patients (4). These rates were crude and not adjusted for potential confounding factors (e.g., age, underlying disease, and severity-of-illness) (5,6). Moreover, the impact of ICU-acquired infection on hospital mortality might be affected by the drug resistance of pathogens (7).

In July 2000, Japanese Ministry of Health, Labour, and Welfare started the Japanese Nosocomial Infection Surveillance (JANIS) System, which consists of three components of ICU, laboratory, and hospitalwide surveillance (8,9,10). In the ICU component, all of the patients admitted to the participating ICUs are followed up until hospital discharge. By using the large cohort database of the JANIS System, we elucidated

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Table 1 Age and sex distribution of the study population

		All	Age, y.o.							
			16–24	25–34	35–44	45–54	55–64	65–74	75–84	85–
All	Alive	6070	190	246	347	826	1339	1922	1035	165
	Dead	1304	31	54	54	164	232	376	292	101
	% of dead	17.7%	14.0%	18.0%	13.5%	16.6%	14.8%	16.4%	22.0%	38.0%
Men	Alive	3934	98	145	218	583	929	1279	608	74
	Dead	828	16	29	38	118	150	246	173	58
	% of dead	17.4%	14.0%	16.7%	14.8%	16.8%	13.9%	16.1%	22.2%	43.9%
Women	Alive	2136	92	101	129	243	410	643	427	91
	Dead	476	15	25	16	46	82	130	119	43
	% of dead	18.2%	14.0%	19.8%	11.0%	15.9%	16.7%	16.8%	21.8%	32.1%

factors associated with hospital mortality in ICU patients and evaluated the impact of ICU-acquired infection on hospital mortality in the context of the drug resistance of pathogens.

Subjects and Methods

A large cohort database was accumulated from the JANIS System (11). Details of data collection and definitions in the JANIS System have been described elsewhere (8,11,12). For all of the patients admitted to the 34 participating ICUs (mostly in national university hospitals) between July 2000 and May 2002, the following patient data were collected using a specific database-oriented software in the standardized forms: sex, age, underlying disease, severity-of-illness (APACHE II score (13)), ICU admission and discharge (date, time, and route), operation (elective and urgent), device use (ventilator, urinary catheter, and central venous catheter), infection (pneumonia, urinary tract infection, catheter-related bloodstream infection, sepsis, wound infection, and others), and hospital discharge (date and outcome). All types of infection were diagnosed according to the JANIS criteria (14). ICU-acquired infection was defined as a newly developed infection at least 2 days after ICU admission (15).

The cohort consisted of 7,374 eligible patients, aged 16 years or older, who stayed in ICU for 48 to 1,000 hours, did not transferred to another ICU, and did not become infected within 2 days after ICU admission. They were followed up until hospital discharge or to Day 180 after ICU discharge. Table 1 shows the age and sex distribution of the 7,374 ICU patients.

We paid special attention to the protection of anonymity and the confidentiality of the available data.

Statistical analyses

The statistical analyses were performed with the Statistical Analysis Systems (SAS, version 8.2). Distributions of operation, device use, and ICU-acquired infections were compared by chi-square tests. Adjusted hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated using Cox's proportional hazard model (16).

Results

Table 2 shows the relationship between operation or device use and hospital mortality. Compared with those who had no operation, those who had elective or urgent operations showed significantly lower rates of hospital mortality. The use of a ventilator or a central venous catheter was significantly associated with hospital mortality, while that of a urinary catheter was not.

Table 2 Relationship between operation or device use and hospital mortality

	Alive	Dead	% of dead	
[Operation]				
None	2175	756	25.8%	
Elective	2542	181	6.6%	
Urgent	1353	367	21.3%	p<0.001
[Ventilator]				
Non-user	2067	210	9.2%	
User	4003	1094	21.5%	p<0.001
[Urinary catheter]				
Non-user	275	75	21.4%	
User	5795	1229	17.5%	p=0.06
[Central venous catheter]				
Non-user	1457	198	12.0%	
User	4613	1106	19.3%	p<0.001

Distributions were compared by chi-square tests.

Table 3 shows the relationship between ICU-acquired infection and hospital mortality. Overall, 678 patients (9.2%) had at least one episode of ICU-acquired infection. Drug-resistant pathogens were detected in 201 patients. The most common ICU-acquired infections were pneumonia (517 cases, 64%), followed by sepsis (106 cases, 13%), wound infection (102 cases, 13%), urinary tract infection (43 cases, 5%), and catheter-related bloodstream infection (42 cases, 5%). All types of ICU-acquired infection were significantly associated with hospital mortality. Compared with those who had no infection, those who had ICU-acquired infections caused by drug-susceptible and -resistant pathogens showed higher rates of hospital mortality. The rate of ICU-acquired infection caused by drug-resistant pathogens was higher than that by drug-susceptible pathogens, except for urinary tract infection, in which few cases of drug-resistant pathogens were observed.

Table 4 shows the HRs and the corresponding 95% CIs for hospital mortality. After adjusting for sex, age, and APACHE II score, a significantly higher HR for hospital mortality was found in ventilator use, central venous catheter use, and ICU-

Table 3 Relationship between ICU-acquired infection and hospital mortality

	Alive	Dead	% of dead	
[All]				
None	5656	1040	15.5%	
Drug-susceptible	305	172	36.1%	
Drug-resistant	109	92	45.8%	p<0.01
[Pneumonia]				
None	5756	1101	16.1%	
Drug-susceptible	230	140	37.8%	
Drug-resistant	84	63	42.9%	p<0.001
[Urinary tract infection]				
None	6042	1289	17.6%	
Drug-susceptible	25	15	37.5%	
Drug-resistant	3	0	0.0%	p<0.01
[Catheter-related bloodstream infection]				
None	6049	1277	17.4%	
Drug-susceptible	18	18	50.0%	
Drug-resistant	3	3	50.0%	p<0.001
[Sepsis]				
None	6038	1230	16.9%	
Drug-susceptible	24	52	68.4%	
Drug-resistant	8	22	73.3%	p<0.001
[Wound infection]				
None	6009	1263	17.4%	
Drug-susceptible	44	28	38.9%	
Drug-resistant	17	13	43.3%	p<0.001

Distributions were compared by chi-square tests.

Table 4 Hazard ratios and the corresponding 95% confidence intervals for hospital mortality

	HR	95% CI (lower–upper)
Sex (Women vs. Men)	1.06	(0.95–1.19)
Age, y.o. †		
45–54	1.19	(0.94–1.49)
55–64	1.06	(0.85–1.31)
65–74	1.11	(0.91–1.35)
75–	1.33	(1.09–1.62)
APACHE II score ‡		
11–15	1.68	(1.37–2.06)
16–20	2.66	(2.18–3.25)
21–25	4.28	(3.48–5.27)
26–30	5.92	(4.76–7.37)
31–	7.88	(6.23–9.97)
Operation		
Elective	0.29	(0.24–0.34)
Urgent	0.68	(0.59–0.77)
Ventilator	1.78	(1.49–2.12)
Urinary catheter	0.70	(0.54–0.90)
Central venous catheter	1.23	(1.04–1.47)
ICU-acquired infection		
Drug-susceptible	1.11	(0.94–1.31)
Drug-resistant	1.42	(1.15–1.77)

HR=hazard ratio, CI=confidence interval.
† compared with –44 y.o.
‡ compared with 0–10.

acquired infection caused by drug-resistant pathogens, with a significantly lower HR in elective or urgent operations and urinary catheter use. The impact of ICU-acquired infection on hospital mortality was different between drug-susceptible pathogens (HR 1.11, 95% CI: 0.94-1.31) and drug-resistant pathogens (HR 1.42, 95% CI: 1.15-1.77).

Discussion

By using the large cohort database of the JANIS System, we elucidated factors associated with hospital mortality in ICU patients and evaluated the impact of ICU-acquired infection on hospital mortality in the context of the drug resistance of pathogens. To our knowledge, this is the fist multicenter cohort study on hospital mortality in ICU patients in Japan. The JANIS System attempts to provide a uniform approach of data collection and definitions to participating ICUs. Data are collected using a specific database-oriented software in the standardized forms. All types of infection are diagnosed according to the JANIS criteria. Thanks to the JANIS database, we may further obtain reliable findings from standardized data.

The crude hospital mortality rate in the patients with ICU-acquired infection caused by drug-susceptible and -resistant pathogens was 36.1% and 45.8%, respectively, against 15.5% of that in the non-infected patients (Table 3). These rates are somewhat higher than those shown in another cohort study of 28 ICUs in 8 countries (32.1% in patients with ICU-acquired infection and 12.1% in non-infected patients)(4). Because of the difference in ICU type (surgical unit dominant vs. medical unit dominant), minimal length of ICU stay (48 hours vs. 24 hours), and other settings between the two studies, it is difficult to compare the rates in detail. Multivariate analysis, adjusting for sex, age, and APACHE II score, showed that the risk of hospital mortality in the patients with ICU-acquired infection caused by drug-resistant pathogens was 1.4 times higher than that in the non-infected patients (Table 4). This result supports the importance of preventive measures against ICU-acquired infections, especially those caused by drug-resistant pathogens.

The EPIC study showed that the impact of ICU-acquired infection on ICU mortality might vary according to type of infection; the highest odds ratio was found in sepsis (3.50), followed by pneumonia (1.91) and bloodstream infection (1.73) (3). Moreover, several studies showed that inadequate administration of autibiotics might be an important determinant of hospital mortality (17,18). When we evaluated the impact of ICU-acquired infection on hospital mortality in the context of types of infection, only sepsis was significantly associated with a high risk of hospital mortality (HR 2.14, 95% CI:1.62-2.84) (data not shown). The impact of ICU-acquired infection on hospital mortality, as well as that on ICU mortality, might vary according to type of infection. In the future, the increase in the risk of hospital mortality in patients with ICU-acquired infection will be evaluated in detail, taking into account type of infection and antibiotics use in addition to the drug resistance of pathogens.

In the multivariate analysis, the risk of hospital mortality was increased in those aged 75 years or older and also increased

with APACHE II score. These results support the importance of adjustment for age and severity-of-illness as major confounding factors.

The risk of hospital mortality in those who had elective or urgent operations was lower than that in those who had no operation. Those who had operations were likely to have a better physical strength before ICU administration. Moreover, some other factors (e.g., underlying disease, preoperative antibiotics use, and length of ICU stay) (19) might contribute to the low risk of hospital mortality in those who had operations.

Each device use was significantly associated with hospital mortality. The risks of hospital mortality in users of ventilators and central venous catheters were 1.8 and 1.2 times higher than that in non-users. Because we could not take into account duration of device use, the impact of device use on hospital mortality might be underestimated or overestimated. Those who use a device are likely to be in a severe condition. Moreover, the longer a device is used, the more likely it is to cause infections (20). In this study, the utilization rates of ventilator and central venous catheter were increased with APACHE II score (Table 5). Also, ICU-acquired infections were more frequently observed in users of ventilator and central venous catheter (Table 6). Because both APACHE II score and ICU-acquired infection were simultaneously incorporated into Cox's proportional hazard model, their confounding effects might be minimized. However, the impact of ICU-acquired infection on hospital mortality might be underestimated or overestimated. Further studies, such as path analysis, may help in the understanding of the details of the relationships in terms of cause and effect among device use, APACHE II score, ICU-acquired infection, and hospital mortality. Contrary to our expectation, the risk of hospital mortality in users of urinary catheter was lower than that in non-users. It might be an apparent relationship caused by the high utilization rate of urinary catheter (95%). It is difficult to explain the low risk in users of urinary catheter and to find a conclusive answer on the relationship between urinary catheter use and hospital mortality based on the finding of this study. When we performed the multivariate analysis again, excluding urinary catheter use from Cox's proportional hazard model, there was no marked difference in the impact of ICU-acquired infection on hospital mortality (data not shown).

This study may provide valuable information on hospital mortality in ICU patients in Japan. However, most of the participating ICUs are in national university hospitals, where the levels of hospital infection control are likely to be higher in Japan. The findings of this study may not represent the average for Japanese hospitals. Further studies may be required to confirm our findings in other hospitals.

In addition to the factors examined in this study, a number of factors have been found to be associated with hospital and ICU mortality. Underlying diseases (e.g., renal failure, acute respiratory failure, coma, neurologic disease) and medical treatments (e.g., steroids or chemotherapy) have been associated with increased hospital mortality (19,21). As mentioned above, inadequate treatment of infections might be an important determinant of hospital mortality (17,18). Medical ICU patients have a higher hospital mortality rate than surgical ICU patients (19). Some ICU organizational characteristics have been found to be associated with hospital mortality (22). A systematic review showed that high-intensity ICU physician staffing (i.e., the intensivist is the patient's primary attending physician, or, the intensivist is not the patient's primary physician, but every patient receives a critical care consultation) was associated with reduced hospital mortality (23). Currently, we are proceeding with a review of the JANIS System and an upgrade of its

Table 5 Relationship between device use and APACHE II score

	APACHE II score						
	0–10	11–15	16–20	21–25	26–30	31–	
[Ventilator]							
Non-user	1322	548	238	107	42	20	
User	1677	1261	973	601	366	219	
% of user	55.9%	69.7%	80.3%	84.9%	89.7%	91.6%	p<0.001
[Urinary catheter]							
Non-user	130	62	64	42	29	23	
User	2869	1747	1147	666	379	216	
% of user	95.7%	96.6%	94.7%	94.1%	92.9%	90.4%	p<0.001
[Central venous catheter]							
Non-user	865	354	230	124	60	22	
User	2134	1455	981	584	348	217	
% of user	71.2%	80.4%	81.0%	82.5%	85.3%	90.8%	p<0.001

Distributions were compared by chi-square tests.

Table 6 Relationship between device use and ICU-acquired infection

	ICU-acquired infection			% of infection	
	None	Drug-susceptible	Drug-resistant		
[Ventilator]					
Non-user	1296	59	22	5.9%	
User	4500	418	179	11.7%	p<0.001
[Urinary catheter]					
Non-user	323	18	9	7.7%	
User	6373	459	192	9.3%	p=0.6
[Central venous catheter]					
Non-user	1581	59	15	4.5%	
User	5115	418	186	10.6%	p<0.001

Distributions were compared by chi-square tests.

database. We will be able to study further details of the risk of hospital mortality in ICU patients.

In conclusion, the use of a ventilator or a central venous catheter, and ICU-acquired drug-resistant infection are associated with a high risk of hospital mortality in ICU patients. The potential impact on hospital mortality emphasizes the importance of preventive measures against ICU-acquired infections, especially those caused by drug-resistant pathogens. Because drug resistance is largely due to inadequate administration of antibiotics, clinicians should consider drug resistance as part of their routine treatment plans (1,2,20). Quality control of antibiotics use by providing locally adapted guidelines for prudent antibiotics use is recommended (2). As a matter of course, basic infection control practices are indispensable to combat the spread of drug-resistant infections (1,20,24). Surveillance systems contribute to detecting drug-resistant infections, feedback on infection control performance, and promoting research to prevent drug-resistant infections. Paying careful attention to this problem at the local ICU level, using a multidisciplinary approach, will have the greatest likelihood of limiting the development and spread of drug-resistant infections (24).

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