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Circadian Rhythm of Hospital Death: Difference Between the Intensive Care Unit and General Room

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ABSTRACT

Background and Objectives: The purpose was to record the time at which biological phenomena stop in different hospital wards and determine regular patterns in times of death, as well as any associated factors.

Subjects and Methods: A total of 6,517 inpatients at the Keimyung University Dongsan Medical Center who died between January 2006 and December 2012 were retrospectively enrolled. A comparative analysis was conducted for the mortality distribution between the intensive care unit (ICU) and general wards (GW).

Results: A total of 3,198 (49%) died in the ICU and 3,319 (51%) in the GW. The ICU showed an increase in mortality over the most recent 3 years. There was no difference in monthly or daily pattern. ICU mortality peaked at 14:00 to 16:00 hours (9.2%) and 20:00 to 22:00 hours (9.1%), and GW mortality peaked at 06:00 to 08:00 hours (9.6%) and 10:00 to 12:00 hours (9.4%), with a significant statistical difference between the two wards (p=0.03). Patients with diseases of the circulatory system died most often in the ICU (28.3%), whereas those with neoplasms had the highest mortality rate in the GW (77.7%) (p<0.01).

Conclusion: Some differences between the ICU and GW may be accounted for by a preserved circadian rhythm that was affected by disease distribution, hospital room environment, and use of various drugs.

Key Words: ▪Circadian Rhythm ▪Chronobiology ▪Mortality

Introduction

Due to the rotation of the Earth, organisms inevitably experience 24 hours of day and night. Due to the day-and-night cycle, or rather the regular change between light and dark, organisms on Earth possess endogenous circadian rhythms, which are vital in adapting to changes in one's environment and sustaining life. Existing research illuminates the effects of changes in the circadian rhythms of animals.[1,2]

The suprachiasmatic nucleus (SCN) of the hypothalamus plays the most important role in the maintenance of the mammalian biological clock.[1,2] The SCN receives photosensitive information through the eyes, and its malfunction completely eliminates rhythms associated with regular sleeping and waking patterns. The retina includes not only regular photoreceptors, which participate in visual perception, but also photosensitive ganglion cells. These cells contain photopigments called melanopsin, through which they detect light. The detected light travels via the retinohypothalamic tract to the SCN, thus affecting biological rhythms. Thus, the SCN receives information regarding the length of day and night via the retina and interprets it, after which it signals the pineal gland of the hypothalamus to secrete melatonin. The melatonin secretion level is at its highest during the night and lowest during the day. Thus, melatonin levels may be said to be indicative of the length of night.

However, centuries of civilization and industrialization, and changes in human living patterns and hobbies are speculated to have brought about a change of behavior in daily, weekly, and even yearly activities, and thus caused human circadian rhythms to evolve.

Death occurs when biological regulatory functions that maintain homeostasis stop working. Existing studies suggest that circadian rhythms and biological clocks may affect homeostasis, although results of previous research do not show consensus.

The purpose of the present study was to record the time at which biological phenomena stop in different hospital wards and determine regular patterns in times of death, as well as any associated factors.

Subjects and Methods

This is a retrospective study in which the subjects consisted of 6,517 inpatients at the Keimyung University Dongsan Medical Center who died between January 2006 and December 2012. A comparative analysis was conducted for the mortality distribution between the intensive care unit (ICU) and general wards (GW) according to year, month, day of week, hour of day, disease entity, and age and sex of the patients. We collected the data on all deaths in the ICU and GW for 7 years and used a cross analysis process, which shows absolute numbers and proportions, for comparison of the wards. The flow of mortality in the ICU and GW was analyzed using annual, monthly, and weekly data. The daily pattern of death was divided by 2-hour periods and the proportion of death by age was divided by decade. The mortality cases in two wards were compared by sex and surgical status, and the format of mortality distribution used International Classification of Disease (ICD) categories.

Statistical analysis

The statistical significance level was set at 5% and all calculations were two-tailed. All categorical variables are expressed as absolute values using the chi-square test as appropriate. The trend line selected was a fifth order polynomial to compare patterns of times of death in the ICU and GW using Excel version 2010. SPSS statistical software version 20.0 (IBM Corp., Released 2011. Armonk, NY) was used for all statistical analyses.

Results

From January 2006 to December 2012, a total of 6,517 patients died, with 3,198 (49%) in the ICU and 3,319 (51%) in the GW. Of the 3,198 (49%) in the ICU, 433 (13.7%) died in 2010, 468 (14.6%) in 2011, and 489 (15.3%) in 2012. Of the 3,319 in the GW, 495 (14.9%) died in 2010, 470 (14.2%) in 2011, and 447 (13.5%) in 2012 (p=0.06; Table 1). Figure 1 shows a decreasing pattern over the most recent 3 years in the GW, with an increasing pattern in the ICU. Mortality distribution by year is presented with a bar graph in Online supplementary figure 1.

The ICU saw the highest number of deaths in January (9.5%) and September (8.8%), whereas the GW saw the highest number in January (9.1%) and August (9.0%). The ICU saw the highest number of deaths in winter, and the GW in summer, with no statistical difference between the two wards (p-value for season =0.76, p-value for month =0.87; Table 2). Figure 2 shows the trend line of death by months.

When mortality was examined in 1-hour intervals, no statistical difference was found between the two wards (p=0.09). When examined in 2-hour intervals, the ICU peaked in number of deaths at 14:00 to 16:00 hours (9.2%) and 20:00 to 22:00 hours (9.1%), whereas the GW peaked at 06:00 to 08:00 hours (9.6%) and 10:00 to 12:00 hours (9.4%). Examined by 8-hour intervals, the ICU showed a similar number of deaths for morning (from 4 to 12), evening (from 12 to 20) and night (from 20 to 4) hours;

the GW showed peak numbers in the morning hours, with a significant statistical difference between the two wards (*p*-value for 8-hour intervals =0.04, *p*-value for 2-hour intervals =0.03, Table 3). Mortality distribution by hour of day using a trend line is presented in Figure 3. Online supplementary figure 2 shows a bar graph by 8-hour intervals.

Mortality occurred most often in those in their 60s (ICU, 25.7%; GW, 26.2%) and 70s (ICU, 28.5%; GW, 24.2%), with statistical significance (*p*-value for age <0.01; Table 4). However, there was no statistical significance for categorical age (*p*-value for categorical age =0.64, Table 4). Mortality occurred more in men in both groups (ICU, 59.8%; GW, 62.0%), but this effect was not statistically significant (*p*=0.07; Table 5). The highest mortality rate occurred in the ICU on Wednesdays (14.9%), as opposed to

Table 1. Mortality distribution by year

Hospital ward	ICU	GW	Total	*p*-value
Year				0.06
2006	433 (13.5%)	464 (14.0%)	897	
2007	434 (13.6%)	468 (14.1%)	902	
2008	438 (13.7%)	509 (15.3%)	947	
2009	498 (15.6%)	466 (14.0%)	964	
2010	438 (13.7%)	495 (14.9%)	933	
2011	468 (14.6%)	470 (14.2%)	938	
2012	489 (15.3%)	447 (13.5%)	936	
Total	3,198 (100%)	3,319 (100%)	6,517	

GW, general ward; ICU, intensive care unit.

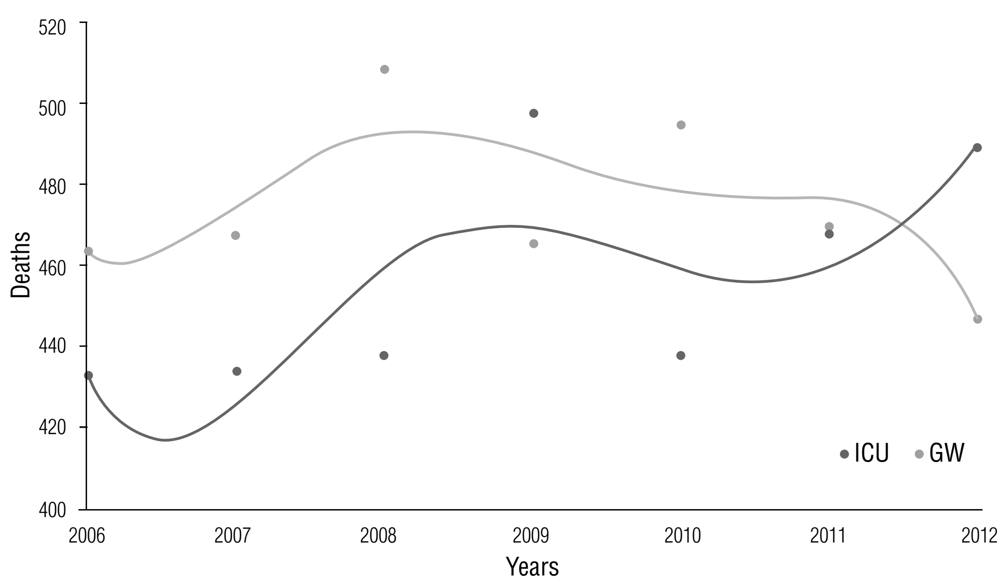

Figure 1. Mortality distribution by year. The number of deaths in the ICU notably increased on a yearly basis.
GW, general ward; ICU, intensive care unit.

Table 2. Mortality distribution by month and season

Hospital ward		ICU		GW		Total		*p*-value
Season	Month							For season 0.76 For month 0.87
Spring	March	804 (25.1%)	305 (9.5%)	833 (25.1%)	301 (9.1%)	1,637	606	
	April		253 (7.9%)		249 (7.5%)		502	
	May		263 (8.2%)		290 (8.7%)		553	
Summer	June	762 (23.8%)	271 (8.5%)	848 (25.6%)	264 (7.9%)	1,605	535	
	July		270 (8.4%)		279 (8.4%)		549	
	August		243 (7.6%)		265 (8.0%)		508	
Autumn	September	809 (25.2%)	240 (7.5%)	801 (24.1%)	283 (8.5%)	1,600	523	
	October		279 (8.7%)		300 (9.0%)		579	
	November		282 (8.8%)		274 (8.3%)		556	
Winter	December	830 (25.9%)	269 (8.4%)	837 (25.2%)	258 (7.8%)	1,667	527	
	January		251 (7.8%)		269 (8.1%)		520	
	February		272 (8.5%)		287 (8.6%)		559	
Total		3,198 (100%)		3,319 (100%)		6,517		

GW, general ward; ICU, intensive care unit.

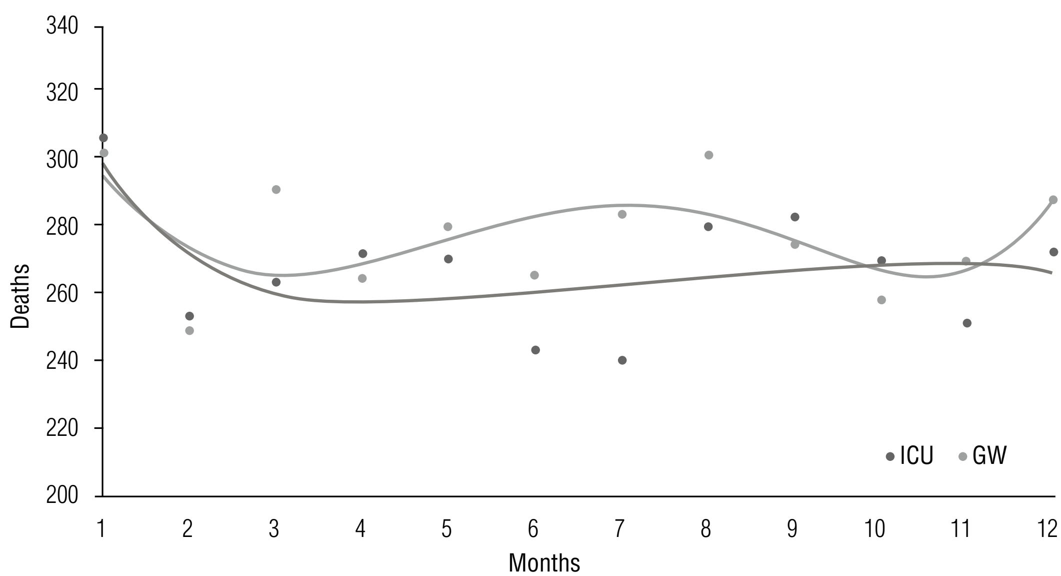

Figure 2. Mortality distribution by month. A monthly analysis showed that mortality rate in the GW was highest in January or July to September.
GW, general ward; ICU, intensive care unit.

Table 3. Mortality distribution by hour of day

Hospital ward		ICU		GW		Total		*p*-value
8-hour interval	2-hour interval							For 8-hour 0.04
Morning	4–6	1,035 (32.8%)	230 (7.2%)	1,212 (36.5%)	303 (9.1%)	2,247	533	For 2-hour 0.03
	6–8		266 (8.3%)		318 (9.6%)		584	
	8–10		252 (7.9%)		279 (8.4%)		531	
	10–12		287 (9.0%)		312 (9.4%)		599	
Day	12–14	1,075 (33.6%)	269 (8.4%)	1,070 (32.2%)	286 (8.6%)	2,145	555	
	14–16		294 (9.2%)		260 (7.8%)		554	
	16–18		265 (8.3%)		270 (8.1%)		535	
	18–20		247 (7.7%)		254 (7.6%)		501	
Night	20–22	1,088 (34.0%)	290 (9.1%)	1,037 (31.2%)	263 (7.9%)	2,125	553	
	22–24		265 (8.3%)		259 (7.8%)		524	
	0–2		277 (8.7%)		245 (7.4%)		522	
	2–4		256 (8.0%)		270 (8.1%)		526	
Total		3,198 (100%)		3,319 (100%)		6,517		

GW, general ward; ICU, intensive care unit.
Morning, 4-12 hour; Day, 12-20 hour; Night, 20-4 hour.

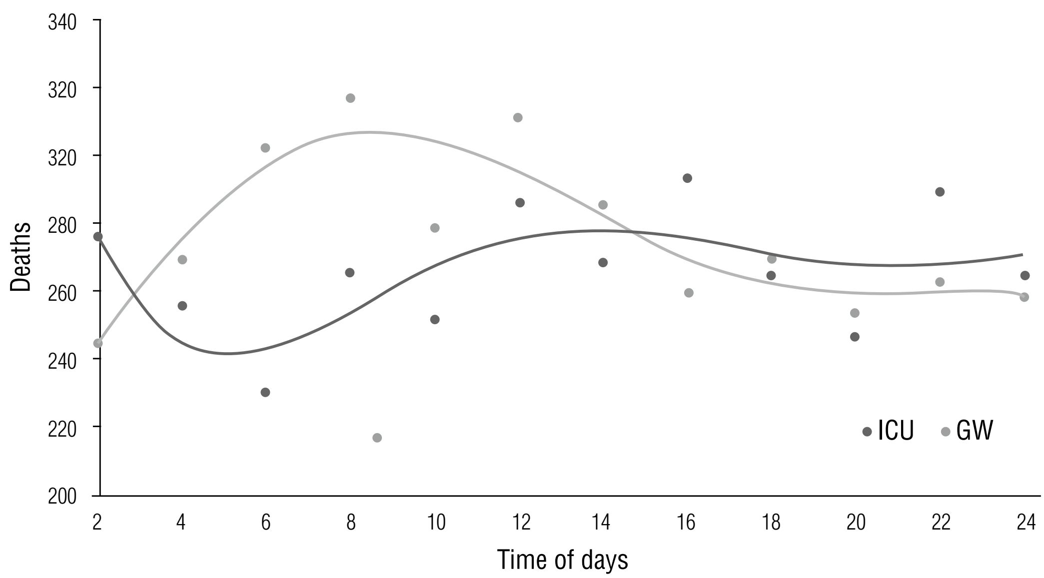

Figure 3. Mortality distribution by hour of day. There is a higher mortality rate in the early morning hours (04:00–06:00 AM) in the GW. GW, general ward; ICU, intensive care unit.

Table 4. Mortality distribution by age

Hospital ward		ICU (63.00±17.24)		GW (60.36±19.61)		Total		*p*-value
Categorical age	Age, years							For categorical age 0.02
Chlidren	0–10	110 (3.4%)	73 (2.3%)	203 (6.2%)	197 (5.9%)	313	270	For age, years <0.01
	11–20		37 (1.1%)		6 (0.2%)		43	
Middle age	21–30	1,852 (57.9%)	52 (1.6%)	2,014 (60.6%)	21 (0.6%)	3,866	73	
	31–40		121 (3.8%)		108 (3.3%)		229	
	41–50		321 (10.0%)		393 (11.8%)		714	
	51–60		536 (16.7%)		622 (18.7%)		1,158	
	61–70		822 (25.7%)		870 (26.2%)		1,692	
Old age	71–80	1,236 (38.7%)	912 (28.5%)	1,102 (33.2%)	824 (24.8%)	2,338	1,736	
	81–90		300 (9.4%)		253 (7.6%)		553	
	91–100		22 (0.7%)		25 (0.8%)		47	
	101–110		2 (0.1%)		0 (0%)		2	
Total		3,198 (100%)		3,319 (100%)		6,517		

GW, general ward; ICU, intensive care unit.
Definition of categorical age: Children, 0-20; Middle age, 20-70; Old age, 70-110.

Table 5. Mortality distribution by sex

Hospital ward	ICU	GW	Total	*p*-value
Sex				0.07
Male	1,914 (59.8%)	2,059 (62.0%)	3,973	
Female	1,284 (40.2%)	1,260 (38.0%)	2,544	
Total	3,198 (100%)	3,319 (100%)	6,517	

GW, general ward; ICU, intensive care unit

Sundays (14.8%) in the GW. This difference was not statistically significant (p=0.60; Table 6). Figure 4 shows the trend line of deaths.

Patients whose diseases fell under ICD group I (diseases of the circulatory system) died most often in the ICU (28.3%), whereas those whose diseases fell under group C (neoplasms) had the highest mortality rate in the GW (77.7%). The difference was statistically significant (p<0.01; Table 7). In both wards, the patients who did not receive surgical treatment had significantly higher mortality than those who did (p<0.01; Table 8).

Discussion

How does time of death differ between hospital wards?

Several interesting facts emerge when mortality rates between 2006 and 2012 in the two hospital wards of the study site are examined. Malignant neoplasms remain the most common cause

Table 6. Morality distribution by day of week

Hospital ward	ICU	GW	Total	*p*-value
Day of week				0.60
Sunday	437 (13.6%)	497 (14.8%)	934	
Monday	451 (14.1%)	460 (13.9%)	911	
Tuesday	455 (14.2%)	484 (14.6%)	939	
Wednesday	476 (14.9%)	461 (13.9%)	939	
Thursday	461 (14.4%)	462 (13.9%)	943	
Friday	459 (14.3%)	447 (13.5%)	906	
Saturday	457 (14.3%)	488 (14.7%)	945	
Total	3,198 (100%)	3,319 (100%)	6,517	

GW, general ward; ICU, intensive care unit

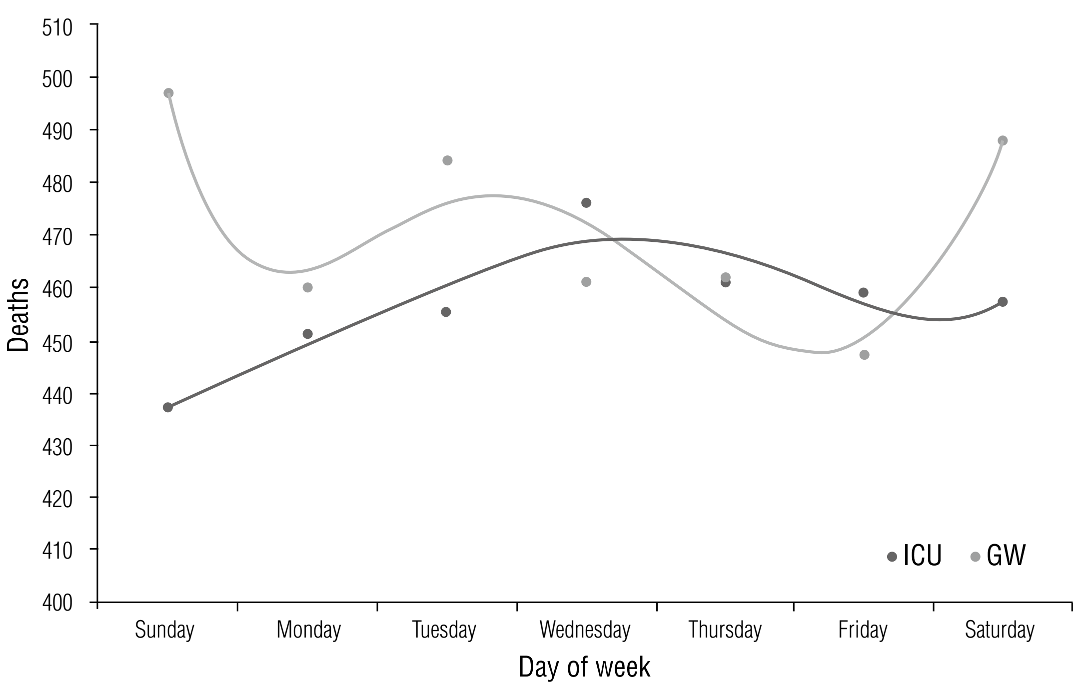

Figure 4. Mortality distribution by day of week. Deaths occur most frequently on weekends for those in the GW, as opposed to those in the ICU, where deaths occur most frequently on weekdays, particularly Wednesdays or Thursdays.
GW, general ward; ICU, intensive care unit.

of death in the GW, in line with many previous findings, whereas diseases of the circulatory system are the most common cause of death in the ICU (Figure 5). Deaths occur most frequently on weekends for those in the GW, as opposed to those in the ICU, in which deaths occur most frequently on weekdays, particularly Wednesdays or Thursdays (Figure 4). The number of deaths in the ICU notably increased on a yearly basis despite advances in medical techniques and information (Figure 1).

According to Rocha *et al.*,[3] malignant neoplasms (42.3%) remain the most common cause of death in the GW, whereas in the ICU, the frequency of septicemia is staggeringly high (64.0%) and the frequency of acute myocardial infarction (AMI) is very low (2.8%). No conclusions have been drawn, but given the high number of deaths due to diseases of the circulatory system in the ICU, the following may be surmised as reasons for the aforementioned trends in mortality: first, a higher ratio of patients

Table 7. Mortality distribution by ICD disease categories

Hospital ward	ICU	GW	Total	*p*-value
Disease group				<0.01
A	154 (4.8%)	37 (1.1%)	191	
B	17 (0.5%)	8 (0.2%)	25	
C	686 (21.4%)	2,579 (77.7%)	3,265	
D	25 (0.7%)	27 (0.8%)	52	
E	66 (20.6%)	14 (0.4%)	80	
F	0 (0%)	1 (0.1%)	1	
G	90 (2.8%)	7 (0.2%)	97	
I	906 (28.3%)	113 (3.4%)	1,019	
J	415 (13.0%)	171 (5.2%)	586	
K	308 (9.6%)	106 (3.2%)	414	
L	10 (0.3%)	1 (0.1%)	11	
M	31 (1.0%)	9 (0.2%)	40	
N	124 (3.8%)	30 (0.9%)	154	
O	6 (0.2%)	0 (0%)	6	
P	35 (1.0%)	181 (5.5%)	216	
Q	13 (0.4%)	15 (0.4%)	26	
R	13 (0.4%)	4 (0.1%)	17	
S	221 (6.9%)	5 (0.1%)	226	
T	75 (2.3%)	11 (0.2%)	226	
Z	3 (0.1%)	0 (0%)	3	
Total	3,198 (100%)	3,319 (100%)	6,517	

GW, general ward; ICU, intensive care unit.
A, B: Certain infectious and parasitic diseases; C: neoplasms; D: blood and hematopoiesis; E: endocrine and metabolism; F: mental and behavioral disorders; G: nervous system; H: eye, adnexa, ear, and mastoid process; I: circulatory system; J: respiratory system; K: digestive system; L: skin and subcutaneous tissue; M: musculoskeletal system; N: genitourinary system; O: pregnancy and childbirth; P: perinatal period; Q: congenital malformations, deformations, and chromosomal abnormalities; R: miscellaneous; S, T: injury, poisoning, and external causes; U: codes for special purposes; V, Y: external causes of morbidity and mortality; Z: factors influencing health status and contract with health services.

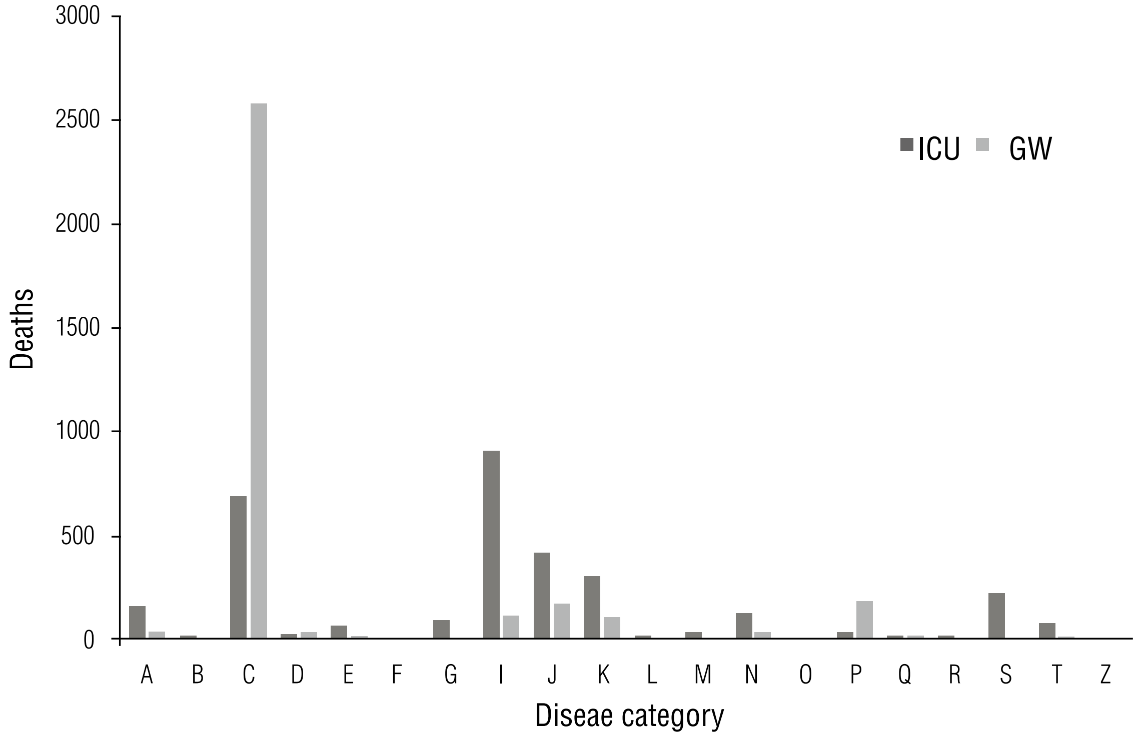

Figure 5. Mortality distribution by ICD categories. Malignant neoplasms remain the most common cause of death in the GW, in line with many previous reports, whereas diseases of the circulatory system are the most common cause of death in the ICU.
ICD, International Classification of disease; GW, general ward; ICU, intensive care unit.
A, B: Certain infectious and parasitic diseases; C: neoplasms; D: blood and hematopoiesis; E: endocrine and metabolism; F: mental and behavioral disorders; G: nervous system; H: eye, adnexa, ear, and mastoid process; I: circulatory system; J: respiratory system; K: digestive system; L: skin and subcutaneous tissue; M: musculoskeletal system; N: genitourinary system; O: pregnancy and childbirth; P: perinatal period; Q: congenital malformations, deformations, and chromosomal abnormalities; R: miscellaneous; S, T: injury, poisoning, and external causes; U: codes for special purposes; V, Y: external causes of morbidity and mortality; Z: factors influencing health status and contract with health services.

have cardiovascular complications compared with those with noncardiovascular complications. Second, patients may often develop multiple organ failure as well as increased diversity of disease as a result of an increased length of stay in the ICU, and thus die owing to inevitable comorbidity with cardiovascular diseases.

Why are ICU deaths increasing?

Reasons for the decreasing trend in the number of deaths in the GW after 2008 in contrast with the increasing number in the ICU may include ICU expansion, increased circulatory and respiratory disease as a result of an increase in nosocomial infections and antibiotic-resistant bacteria, and the increased prevalence of infectious diseases in older patients. However, a multifaceted statistical analysis for yearly trends in the cause of death may reveal a more precise reason for this effect.

Why does the distribution of diseases differ between the ICU and GW?

As previously mentioned, this is in line with previous research showing that malignant neoplasms are the reason for many deaths in the GW. However, in the ICU, patients have complex causes of death, as they not only have malignant neoplasms but also comorbid circulatory, respiratory, and gastroenterological diseases (Figure 5). Therefore, the results of various studies may differ regarding this topic.

Table 8. Mortality distribution by surgical status

Hospital ward	ICU	GW	Total	*p*-value
Surgical status				<0.01
Death without surgery	2,535 (79.3%)	3,190 (96.1%)	5,725	
Death after surgery	663 (20.7%)	129 (3.9%)	792	
Total	3,198 (100%)	3,319 (100%)	6,517	

GW, general ward; ICU, intensive care unit.

How does mortality rate change in different months?

Management of medical personnel affects the mortality rate in a hospital. Another study reported that in-hospital mortality rates are affected by human resource management systems.[4] Moreover, mortality rates increase when resident doctors first begin in-hospital work.[5] At the site of the present study, a monthly analysis showed that the mortality rate in the GW was highest in January or July to September, which were time periods corresponding with January and August staff vacations and redistribution of medical personnel (Figure 2). Meanwhile, no statistical significance (p=0.87) was found between the mortality rate in the months of March to May (ICU, 25.1%; GW, 25.0%) and September to November (ICU, 25.0%; GW, 24.2%), although this appeared to be influenced by the aforementioned management of medical personnel.

How does mortality rate change by different days of the week and time of day?

Differences in mortality rates according to time of day or day of the week have been researched most commonly for cardiovascular diseases. A causal relationship between the increase in alpha-sympathetic tone and sudden cardiac deaths in the mornings was demonstrated.[6] Muller *et al.* analyzed the relationship between occurrence of death and the time of day among 2,203 patients in Massachusetts hospitals over the course of a year and proposed two reasons why the incidence of sudden cardiac death was highest from 7:00 AM to 11:00 AM while being lowest at night. First, most cases of sudden cardiac death are due to myocardial infarctions caused by platelet aggregation at atherosclerotic lesions of coronary vessels, as a result of the increase of plaque rupture and coronary arterial tone from increased blood pressure in the morning. Second, fatal arrhythmias are likely to occur in the mornings owing to electrical instability arising from an increase in sympathetic nervous system activity in the morning.[7-9] Mundigler *et al.* analyzed the causal relationship between 6-sulfatoxy-melatonin (aMT6s), a metabolite of melatonin, and circadian rhythms, and found that urinary aMT6s excretion was reduced in ICU patients, as opposed to GW patients, who maintained regular aMT6s excretion and thus preserved their circadian rhythms.[10] In the present study, the high mortality rate in the early morning hours (04:00–06:00 AM) in the GW may be corroborated by studies such as those previously mentioned (Figure 3). The reason for the lack of such an effect in the ICU may be that endogenous circadian rhythms are changed as the excretion of melatonin from the pineal gland is affected by the use of various sympathomimetic and sedative drugs, as well as the environment of a hospital ward, in which daytime and nighttime differences are unclear. Hourly melatonin secretion levels were not measured in the present study, but future studies may be able to analyze the mortality rate differences between the ICU and GW by investigating the causal relationship between melatonin secretion and circadian rhythms.

The present study showed that in the GW, high mortality rates occurred on weekends, whereas in the ICU, higher mortality rates occurred on Wednesdays and Thursdays (Figure 4). Although not many studies have analyzed inpatient mortality rates based on the day of the week, outpatients and inpatients may still be considered to possess similar circadian rhythms, under the assumption that circadian rhythms are relatively well preserved in GW patients in comparison with ICU patients. This contradicts other studies that stated that outpatient sudden cardiac deaths occur most frequently on Mondays, as such deaths are cardiovascular events arising from the emotional stresses related to the start of a new week.[11] It may thus be the case that despite being in the GW, inpatients still show changes in circadian rhythms in comparison to outpatients, owing to changes in living patterns arising from hospital admittance, unfamiliar hospital environments, and changes in endogenous hormone secretion that result from the diagnoses and treatments of various diseases. Meanwhile, Lopez *et al.* reported that a high number of outpatient sudden cardiac arrests occurred on Wednesdays, although the causes have not yet been identified.[12] Witte *et al.* cited geographical factors for this difference.[11] For instance, Ku *et al.* studied day-of-week differences in a Chinese population admitted to a coronary care unit for AMI and reported that the incidence rate on Sundays was relatively low and that no peak incidence was seen on Mondays.[13] Furthermore, another study on the incidence rate of AMI among a Chinese population showed that the rate was highest on Saturdays, with statistical significance.[14] In a Japanese population, the weekly and monthly changes in terms of aortic dissection incidence showed no clear difference between the days of the week.[15] Thus, race may also be a factor involved in differences in circadian rhythms.

Neumann *et al.* analyzed the hourly, weekly, and monthly mortality rates of terminal cancer patients, and found that rates between 08:00 and 10:00 hours and 16:00 and 18:00 hours were higher than those in night hours. The causes may be related to an increase in platelet aggregation, hypercoagulability, and catecholamine secretion, which are all related to sudden cardiac death. Weekly and monthly comparisons between mortality rates showed unclear results.[16]

The differences in the time-of-day, day-of-week, and monthly patterns of mortality rates in the ICU and GW may be accounted for by the preservation of circadian rhythms in GW patients, due to their having fewer disturbances in endogenous hormones and physiological changes. Meanwhile, the changes in the circadian rhythms of the ICU patients might have been caused by the differences in disease distribution, hospital room environments, and use of various drugs. However, further research is needed to precisely determine the cause of the aforementioned effects.

Conclusion

In conclusion, the difference between ICU and GW is notable in diurnal variation. This difference is explained by the presence of preserved circadian rhythm. ICU patients might have been influenced by more factors of environmental change than GW patients, such as differences in disease distribution, hospital room environments, and use of various drugs; therefore, ICU patients show different circadian rhythm than GW patients. However, a limitation of our study is that we did not investigate the direct causation of circadian variation and other factors mentioned above.

Acknowledgments

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