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Effect of do-not-resuscitate orders on patients with sepsis in the medical intensive care unit: a retrospective, observational and propensity score-matched study in a tertiary referral hospital in Taiwan

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ABSTRACT

Objective The aim of this study was to determine whether do-not-resuscitate (DNR) orders affect outcomes in patients with sepsis admitted to intensive care unit (ICU).

Design This is a retrospective observational study.

Participants We enrolled 796 consecutive adult intensive care patients at Kaohsiung Chang Gung Memorial Hospital, a 2700-bed tertiary teaching hospital in southern Taiwan. A total of 717 patients were included.

Main measures Clinical factors such as age, gender and other clinical factors possibly related to DNR orders and hospital mortality were recorded.

Key results There were 455 patients in the group without DNR orders and 262 patients in the group with DNR orders. Within the DNR group, patients were further grouped into early (orders signed on intensive care day 1, n=126) and late (signed after day 1, n=136). Patients in the DNR group were older and more likely to have malignancy than the group without DNR orders. Mortality at days 7, 14 and 28, as well as intensive care and hospital mortality, were all worse in these patients even after propensity-score matching. There were higher Charlson Comorbidity Index in the emergency room, but better outcomes in those with early-DNR orders compared with late-DNR orders.

Conclusions DNR orders may predict worse outcomes for patients with sepsis admitted to medical ICUs. The survival rate in the early-DNR order group was not inferior to the late-DNR order group.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction that is caused by a dysregulated host response to infection and involves complex underlying mechanisms.[1] Sepsis is among the most common causes for admission to intensive care units (ICUs).[2] It also causes a significant proportion of morbidity[3] and mortality. The

Strengths and limitations of this study

► A large amount of consecutive adult patients presenting with sepsis on admission to the medical intensive care unit was surveyed for do-not-resuscitate (DNR) effect.
► Propensity score-matched method was used to decrease the patient selection bias.
► Early- and late-DNR groups were defined and discussed.
► We did not discuss the influence of financial resources adequacy for patient medical expenses in this study.
► We did not discuss cultural and religious beliefs, ethnicity or physician bias.

mortality rate of sepsis has been reported to be around 30%–50% in the ICU.[4 5] The *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016* suggested that intensive care physicians discuss goals of care and prognosis with patients and families. They recommended that goals of care should be incorporated into treatment and end-of-life care planning. Furthermore, goals of care should be addressed as early as feasible.[6]

Do-not-resuscitate (DNR), also known as allow natural death, is a legal order written either within or outside the hospital on a legal form to withhold cardiopulmonary resuscitation (CPR) or advanced cardiac life support, respecting the wishes of a patient. A DNR order is used for hospitalised patients with critically advanced illness. It may be written by physicians to convey the wishes of patients

not to receive CPR in the event of cardiac arrest. Additionally, DNR orders can result from complex interactions between patients, physicians, families, and regional and hospital norms[7–9] regarding end-of-life care.

Some studies have investigated DNR orders in specific patient groups, such as patients with intracerebral haemorrhage (ICH),[10 11] after resuscitation from out-of-hospital cardiac arrest[12] and with acute ischaemic stroke.[13] However, few studies mentioned the influence of DNR orders in patients with sepsis, a life-threatening condition with critically rapid progression.[14] Therefore, we chose to investigate the impact of DNR orders in patients with sepsis admitted to ICUs. We thought to provide more objective data to help patients or their family make the DNR decision.

METHODS
Participants
This retrospective study was conducted from August 2013 to November 2016 through chart review. Furthermore, this study was carried out in the 34 beds of the three medical ICUs at Kaohsiung Chang Gung Memorial Hospital, a 2700-bed tertiary teaching hospital in southern Taiwan. We surveyed consecutive adult patients (aged ≥18 years) who presented with sepsis on admission to the medical ICU from August 2013 to November 2016. We excluded patients who re-admitted to ICU during the study period and also those who left the ICU within 2 days. The enrolled patients were divided into two groups: with DNR orders (DNR group) and without DNR order (without-DNR group) (figure 1). We also defined an
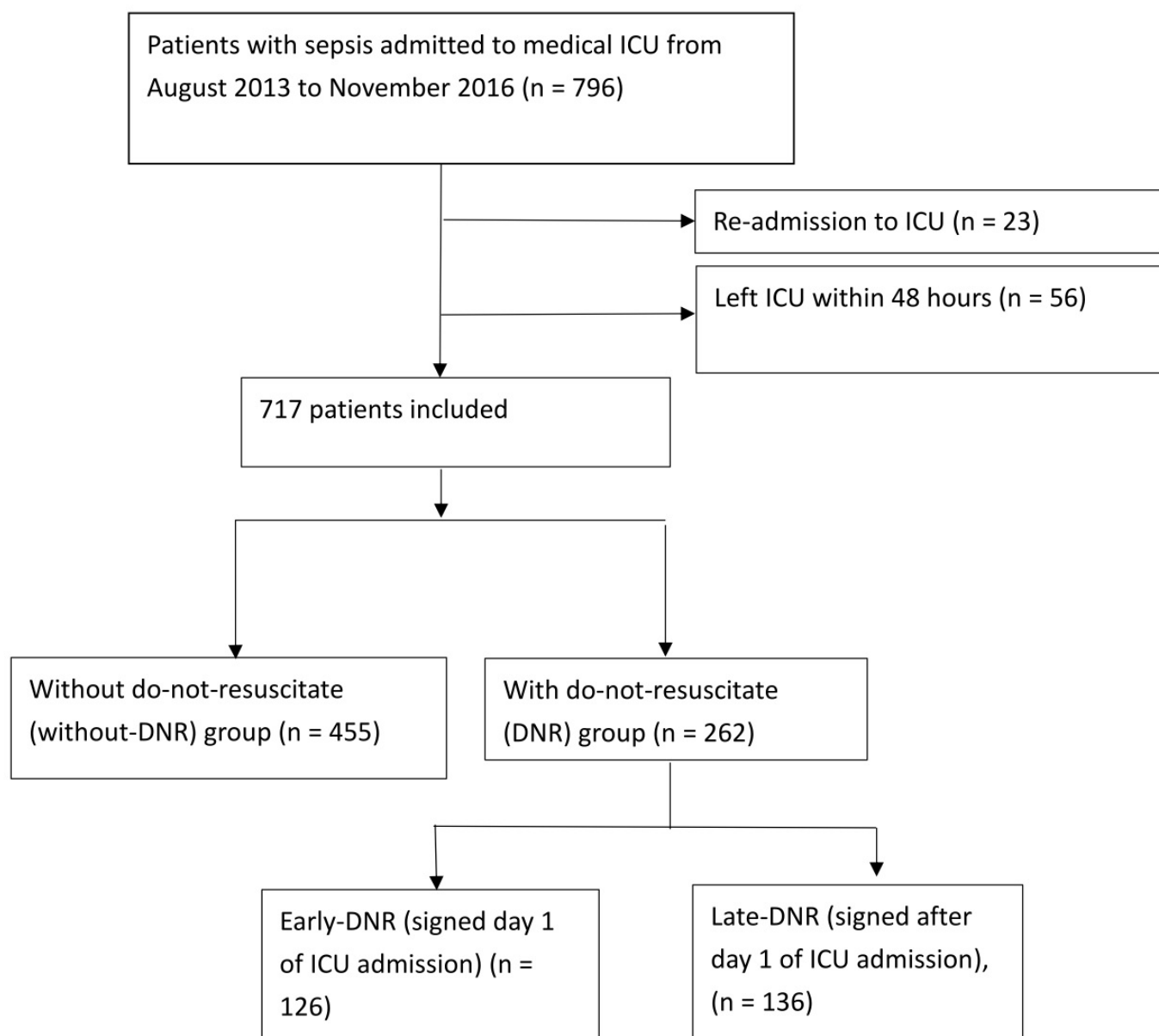
Figure 1 Of the 796 patients with sepsis between August 2013 and November 2016, 717 were included in the final analysis. DNR, do-not-resuscitate; ICU, intensive care unit.

early-DNR group as having DNR consent signed within the first day of ICU admission and a late-DNR group as signing after day 1. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and the requirements for patient consent were waived (201800815B0).

Definitions

DNR means 'do not resuscitate'. A DNR does not affect any treatment other than CPR and endotracheal tube intubation. If signed after the two aforementioned procedures, we keep the patient on ventilator support if withdrawing necessary support is not requested. DNR orders are written instructions from a physician telling healthcare providers not to perform further CPR. The doctor writes the order only after discussing it with the patient (if possible), the proxy or the patient's family.[15] DNR in our study allowed for blood transfusion, vasopressors use and emergent haemodialysis.

According to 'The Third International Consensus Definitions for Sepsis and Septic Shock', sepsis was defined as life-threatening organ dysfunction due to a disproportionate host response to infection.[16–18] Quick Sequential Organ Failure Assessment (qSOFA) criterion was included, such as respiratory rate ≥22/min, altered mentation and systolic blood pressure ≤100 mm Hg.[19] All enrolled patients met the latest criteria for sepsis on admission to ICU.

Data collection

Clinical data were retrieved from medical records, including age, gender, Sequential Organ Failure Assessment (SOFA) score,[20 21] qSOFA score,[19] Acute Physiological Assessment and Chronic Health Evaluation II (APACHE II) score,[22] Charlson Comorbidity Index and underlying comorbidities,[23 24] and other clinical factors possibly related to DNR (discussed below).

Statistical calculations

Categorical variables were analysed using the χ^2 test, and continuous variables were compared using the Mann-Whitney U test. P value <0.05 was considered to indicate a significant result. Univariate analysis was used to identify significant risk factors associated with DNR in this study.[25] Propensity scoring was also used for control of selection bias and performed using binary logistic regression to generate a propensity score for each patient who did or did not sign a DNR. We used Greedy methods with a 0.25×SD calliper width using NCSS 12 software. The standardised mean difference of propensity score was −0.09%.[26] Variables included in the propensity model were age, sex, presence of diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), liver cirrhosis, end-stage renal disease (ESRD), malignancy, APACHE II score, Charlson Comorbidity Index, received intubation and haemodialysis during this admission.[27] After correcting for these confounding factors, ICU

mortality and hospital mortality analyses were repeated. After propensity score matching, we used Wilcoxon signed-rank test for further evaluation. All p values were >0.05.[26] All statistical analyses were performed using the SPSS V.22.0 software package (IBM, released 2013, IBM SPSS Statistics for Windows V.22.0).

Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

RESULTS

Patient characteristics and findings

A total of 717 patients were included in the study. The average age of this cohort was 67.26±14.85 years, with male predominance (59.3%). The DNR group was older by 4.5 years than the without-DNR group (71.5 (60–82) vs 67 (57–77), p<0.001) (table 1). APACHE II score and Charlson Comorbidity Index were worse in the DNR group (p<0.001). Malignancy was found in 22.7% of the overall cohort, whereas in the DNR group, it was 29.4% (table 1). Most of the patients came from emergency department without a signed DNR in place. Additionally, most DNR orders were signed in medical ICUs. The mortality rate seemed high in general, which is consistent with the hospital environment (2700-bed tertiary referral hospital). Sites of suspected infection were listed in table 2.

Propensity-score matching

After propensity-score matching for 14 variates, including age, sex, presence of diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, COPD, liver cirrhosis, ESRD, malignancy, APACHE II score, Charlson Comorbidity Index and receipt of intubation and haemodialysis during this admission, we found 239 paired patient groups (table 1). SOFA score, qSOFA and individual SOFA subscores in the emergency room (ER) on admission day 1 and day 3 in the without-DNR and DNR groups are listed in table 3.

Patients with DNR had worse APACHE II and Charlson Comorbidity Index scores on admission, and they also had worse SOFA scores at ER the admission day 1 and day 3. After propensity-score matching, those severity indices were comparable between the two groups. However, SOFA score appeared to deteriorate in the ICU between admission day 1 and day 3 in the DNR-group patients. SOFA subscores on cardiovascular, Glasgow Coma Scale (GCS) and creatinine or urine output were significantly different between the two groups on ICU admission day 1 and day 3. After propensity-score matching, there were still significant differences in SOFA cardiovascular subscores (table 3). Hospital mortality rate was 39.3% in total, whereas in the DNR group, it was 67.9%. Seven-day mortality, 14-day mortality, 28-day mortality, ICU mortality and hospital mortality were all significantly different between patients with and without DNR, even

Table 1 Without-DNR group versus DNR group before and after propensity-score matching

	Before matching			After matching		
	Without-DNR n=455 (%)	DNR n=262 (%)	P value	Without-DNR n=239 (%)	DNR n=239 (%)	P value
Age, years (median (IQR))*	67 (57–77)	71.5 (60–82)	<0.001	72 (62–79)	70 (59–82)	0.968
Male sex, n (%)	261 (57.4)	164 (62.6)	0.170	153 (64.0)	144 (60.3)	0.452
With malignancy, n (%)	86 (18.9)	77 (29.4)	0.001	64 (26.8)	63 (26.4)	1.000
APACHE II (median (IQR))	20 (16–26)	23 (19–29)	<0.001	22 (18–27)	22 (18–29)	0.904
CCI (median (IQR))	4 (3–6)	5 (4–6)	<0.001	5 (3–6)	5 (4–6)	0.983
Advanced life support, n (%)						
Intubation	410 (90.1)	238 (90.8)	0.750	218 (91.2)	216 (90.4)	0.871
Haemodialysis	83 (18.2)	59 (22.5)	0.166	53 (22.2)	56 (23.4)	0.830
Comorbidities, n (%)						
Hypertension	253 (55.6)	153 (58.4)	0.467	140 (58.6)	137 (57.3)	0.856
Diabetes mellitus	205 (45.1)	115 (43.9)	0.763	110 (46.0)	107 (44.8)	0.850
Cerebrovascular accident	91 (20.0)	49 (18.7)	0.673	46 (19.2)	47 (19.7)	1.000
Coronary artery disease	111 (24.4)	71 (27.1)	0.423	65 (27.2)	65 (27.2)	1.000
COPD	63 (13.8)	40 (15.3)	0.601	39 (16.3)	37 (15.5)	0.897
Liver cirrhosis	35 (7.7)	25 (9.5)	0.389	23 (9.6)	20 (8.4)	0.736
End-stage renal disease	46 (10.1)	29 (11.1)	0.686	25 (10.5)	27 (11.3)	0.885

*We used Mann-Whitney U test for non-normal data before matching, and we used Wilcoxon signed-rank test for hand non-normal data after matching
APACHE, Acute Physiological and Chronic Health Evaluation; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; DNR, do-not-resuscitate.

after propensity-score matching (online supplementary table 1). The Kaplan-Meier curves of ICU and hospital mortalities are shown in figure 2.

Early and late DNR
Patient characteristics in the early-DNR and late-DNR groups were comparable except for a higher proportion of COPD in early-DNR group patients (online supplementary table 2). SOFA and qSOFA scores and individual SOFA subscores are shown in online supplementary table 3. Although they had higher Charlson Comorbidity Index in the ER, better outcomes were noted for the early-DNR

Table 2 Site of suspected infection

Site of suspected infection (n=717)	n (%)
Pneumonia	464 (64.7)
Intra-abdominal infection	54 (7.5)
Urinary tract infection	153 (21.3)
Bacteraemia	53 (7.4)
Skin or soft tissue infection	37 (5.2)
Meningitis	4 (0.6)
Dengue	15 (2.1)
Influenza	4 (0.6)
Infective endocarditis	2 (0.3)
Unidentified	64 (8.9)

group (online supplementary table 3). Kaplan-Meier curves on ICU and hospital mortalities between early DNR and late DNR are shown in figure 3.

DISCUSSION
Sepsis can be considered a battle between pathogens and a host's immune system. It involves a life-threatening organ dysfunction due to a dysregulated host response to infection.[28 29] Due to high mortality when organ dysfunction progresses,[30] some patients with sepsis face detrimental outcomes.[31] Patients who are elderly or who have advanced cancer are much less likely to survive.[32] The DNR request may be made by the patient or their family and allows the medical team who takes care of them to respect their wishes. DNR orders in some situations have been subject to ethical debate. It is reasonable to implement DNR orders in patients with clinical manifestations when an attempt at resuscitation will not be successful. The clinical manifestations of sepsis are variable. They depend on the initial site of infection, the pattern of organ dysfunction, the underlying comorbidities and the interval before initiation of treatment.[33] The implementation of DNR orders may also be influenced by the above manifestations. In our study, the DNR groups did not get less ancillary cares, such as central line, vasopressors, blood transfusion, emergent haemodialysis or surgery. Moreover, palliative care was available in our hospital. If

Table 3 SOFA and qSOFA scores and individual SOFA subscores at ER, admission day 1 and day 3 in without-DNR and DNR groups

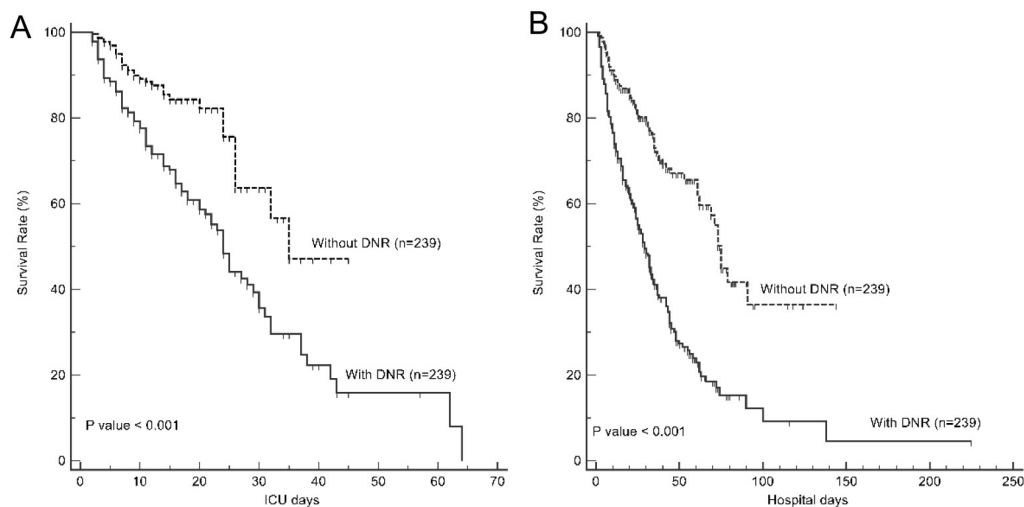|	Before matching			After matching		
Emergency room (median (IQR))*	**Without-DNR (n=455)**	**DNR (n=262)**	**P value**	**Without-DNR (n=239)**	**DNR (n=239)**	**P value**
qSOFA	1 (0–2)	1 (0–2)	0.404	1 (1–2)	1 (1–2)	0.302
SOFA score	7 (5–9)	8 (5–10)	0.006	7 (5–10)	8 (4–10)	0.149
PaO_2/FiO_2 subscore	2 (1–3)	2 (1–3)	0.495	2 (1–4)	2 (1–3)	0.847
Platelet subscore	0 (0–1)	0 (0–1)	0.555	0 (0–1)	0 (0–1)	0.890
Bilirubin subscore	0 (0–0)	0 (0–0)	0.594	0 (0–0)	0 (0–0)	0.491
Cardiovascular subscore	0 (0–1)	0 (0–1)	0.053	0 (0–1)	0 (0–1)	0.173
GCS subscore	2 (0–4)	2 (0–4)	0.313	2 (0–4)	2 (0–4)	0.956
Creatinine or urine output subscore	1 (0–2)	1 (0–2)	0.007	1 (0–2)	1 (0–2)	0.309
Admission day 1						
qSOFA	2 (1–2)	2 (1–2)	0.180	1 (1–2)	2 (1–2)	0.183
SOFA score	8 (6–11)	10 (7–12)	<0.001	8 (6–10)	9 (7–12)	0.001
PaO_2/FiO_2 subscore	2 (1–3)	2 (1–3)	0.206	2 (1–3)	2 (1–3)	0.397
Platelet subscore	0 (0–1)	0 (0–2)	0.952	0 (0–1)	0 (0–2)	0.489
Bilirubin subscore	0 (0–0)	0 (0–1)	0.069	0 (0–0)	0 (0–1)	0.162
Cardiovascular subscore	0 (0–1)	1 (0–4)	<0.001	0 (0–1)	1 (0–4)	<0.001
GCS subscore	3 (2–4)	3 (2–4)	<0.001	3 (2–4)	3 (2–4)	0.172
Creatinine or urine output subscore	1 (0–2)	1 (0–3)	0.007	1 (0–2)	1 (0–3)	0.262
Admission day 3						
qSOFA	1 (1–2)	1 (1–2)	0.003	1 (1–2)	1 (1–2)	0.006
SOFA score	7 (5–9)	8.5 (6–11)	<0.001	7 (4–9)	8 (5–10)	<0.001
PaO_2/FiO_2 subscore	2 (1–2)	2 (1–3)	0.013	2 (1–2)	2 (1–3)	0.032
Platelet subscore	0 (0–2)	1 (0–2)	0.003	0 (0–2)	1 (0–2)	0.005
Bilirubin subscore	0 (0–0)	0 (0–1)	0.009	0 (0–0)	0 (0–1)	0.031
Cardiovascular subscore	0 (0–0)	0 (0–1)	<0.001	0 (0–0)	0 (0–1)	0.001
GCS subscore	3 (2–3)	3 (2–4)	<0.001	2 (2–3)	3 (2–4)	0.033
Creatinine or urine output subscore	0 (0–2)	1 (0–3)	0.010	0 (0–2)	1 (0–3)	0.522

*We used Mann-Whitney U test for non-normal data.
DNR, do-not-resuscitate; ER, emergency room; FiO_2, fraction of inspired concentration of oxygen; GCS, Glasgow Coma Scale; PaO_2, PaO_2 of oxygen; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment.

the patient, proxy or patient's family requested palliative care, we would consult the palliative team for further evaluation. If the condition was suitable for palliative care and the patient, proxy or patient's family agreed, we would start palliative care for the patient.

In our study, the organ dysfunction scored by SOFA score and individual SOFA subscores (including pulmonary, central nervous system, cardiac, renal, liver, platelet) were analysed. We found that patients with DNR had worse APACHE II scores and Charlson Comorbidity Indexes on admission, and they also had worse SOFA scores in the ER. In addition, they had worse SOFA scores on ICU admission days 1 and 3. SOFA subscores on the cardiovascular, GCS and creatinine or urine output were significantly different between the DNR group and the without-DNR group on ICU admission days 1 and 3.

To eliminate these confounders, we adopted propensity-score matching. After propensity-score matching, there were still significant differences between the groups on the SOFA cardiovascular subscore. This suggests that factors related to the SOFA cardiovascular subscore were important influences on the decision of patients or families to sign a DNR.

Unsurprisingly, since the incidence of sepsis increases[34] while the remaining life expectancy decreases with ageing, our data revealed that DNR group patients were older. Underlying comorbidities, especially malignancy, may also influence the outcomes of sepsis. We found that patients with sepsis with underlying active malignancy requiring ICU admission had worse outcomes than those without active malignancy.[35] Furthermore, our data showed that a larger proportion of malignancy was noted

Figure 2 Kaplan-Meier curve of ICU days (A) and hospital days (B) for 239 paired patients after propensity-score matching. DNR, do-not-resuscitate; ICU, intensive care unit.

in the DNR group. As for other comorbidities, we did not find differences between the two groups. Partially due to a healthcare financing system, which supports dialysis therapy with the highest incidence and prevalence of ESRD in the world,[36] patients with sepsis needing haemodialysis were not over-represented in the DNR group. Early DNR orders could compromise the outcome of patients with sepsis due to delay in the interval before initiation of treatment. However, with higher Charlson Comorbidity Index in the ER, there were better outcomes in the early-DNR group than the late-DNR group. This suggests that a DNR does not affect any treatment other than CPR in clinical practice. This finding may reassure patients reaching the decision for themselves or family members regarding a DNR. In this study, we found DNR orders independently associated with higher mortality rates, including 7-day, 14-day, 28-day, ICU and hospital mortalities. The phenomenon persists even after propensity-score matching for age, sex, presence of diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, COPD, liver cirrhosis, ESRD, malignancy, APACHE II score, Charlson Comorbidity Index,

received intubation and haemodialysis during this admission. This finding suggests that patients with a DNR may have a different course overall within the hospital.

In our country, DNR orders before hospitalisation are not very popular. DNR orders are usually written instructions from a physician informing healthcare providers not to perform CPR. The doctor writes the order only after discussing it with the patient (if possible), the proxy or the patient's family.[15] Based on this study, we can provide doctors with more objective data to discuss with patients' families about DNR. This step may allow family members to be more psychologically prepared to accept that the patient is at increased risk of mortality. This, in turn, may help comfort a grieving family member. Some studies revealed that early DNR orders are associated with a decrease in potentially critical hospital interventions and procedures, as well as in survival to discharge in resuscitation from out-of-hospital cardiac arrest patients.[12] However, it was also pointed out that, in the absence of prior patient wishes, DNR assignment within 24 hours may be premature given the lack of early prognostic indicators. It is a different story for sepsis. The diversity of
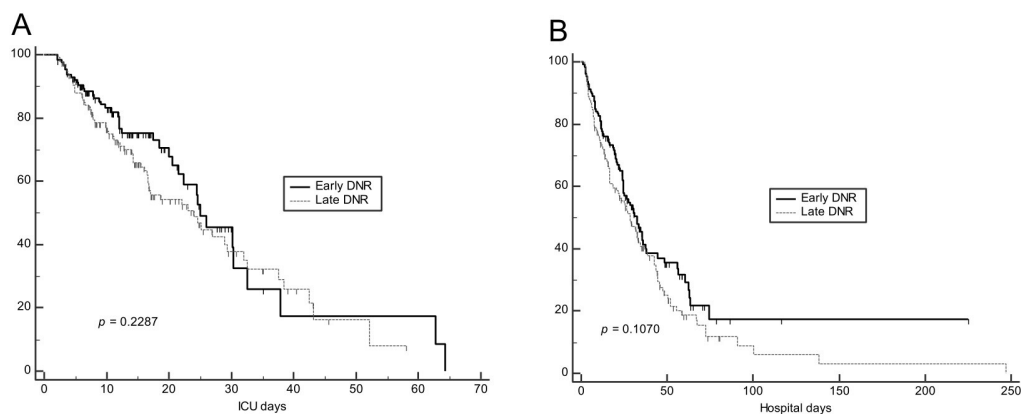
Figure 3 Kaplan-Meier curves for ICU mortality (A) and hospital mortality (B) in early-DNR and late-DNR groups. DNR, do-not-resuscitate; ICU, intensive care unit.

causes of sepsis makes it more difficult to evaluate the impact of early DNR in patients with sepsis. In the present study, patients with early DNR had no significant difference in short-term mortality and in fact showed a better trend compared with late DNR. In a previous study about DNR orders in patients with intracerebral haemorrhage (ICH), DNR orders were not commonly used for patients with ICH in this Chinese sample. No relationship between ICH severity and DNR decision-making was observed.[10] That study focused on an Asian population with a DNR rate of 8.4%. However, in our study, we collected the studied patient data from August 2013 to November 2016. During these years, the health institutes provided many education courses for the population on the meaning of DNR. The DNR rate was 36.5% in a total of 717 patients in our study. Additionally, patients and families were more aware of terminal illnesses other than malignancy, such as late-stage COPD. In our study, we found that patients with COPD with CO_2 retention were more prone to early than late DNR. According to the study of Phua et al, physicians in ICUs in Asia reported that they were less likely to limit life-sustaining treatments at the end of life than Western physicians. In addition, attitudes and reported practice varied widely across countries and regions.[37] There were multiple factors associated with variations in reported practices, including economic, cultural, religious and legal differences, as well as personal attitudes and many others. Our results add to the field of information that the outcomes of early DNR were not inferior to that of late DNR, which may affect clinical practice.

CONCLUSION

DNR could be a predictor for worse outcomes of patients with sepsis admitted to medical ICUs. Patients with underlying malignancy, older patients and those with higher sepsis severity scores were more prone to request DNR. The survival rate in the early-DNR group was not inferior to that in the late-DNR group.

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