

## The Effect of Early Cardiopulmonary Rehabilitation on the Outcomes of Intensive Care Unit Survivors

**Short title:** Outcomes of rehabilitation on intensive care unit survivors

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**Abstract:** Background: This study aims to compare the impact of early and late post-discharge cardiopulmonary rehabilitation on the outcomes of intensive care unit (ICU) survivors. Methods: The retrospective, cohort study used a sub-database of the Taiwan National Health Insurance Research Database (NHIRD) that contains information of all patients had ICU admission between 2000 and 2012. Early group was defined if patients had received cardiopulmonary rehabilitation within 30 days after ICU discharge, and late group was define as if patients had received cardiopulmonary rehabilitation between 30 days and one year after ICU discharge. The end points were mortality and re-admission during the 3-year follow-up. Results: Among 2136 patients received cardiopulmonary rehabilitation after ICU discharge, 994 was classified early group and other 1142 patients were classified as late group. Overall, early group had a lower mortality rate (6.64% vs 10.86%,  $p = 0.0006$ ), and a lower ICU readmission rate (47.8% vs 57.97%,  $p < 0.0001$ ) than late group after 3-year follow-up. Kaplan-Meier analysis showed that early group had significantly lower mortality ( $p=0.0009$ ) and readmission rate ( $p<0.0001$ ) than late group. In multivariate analysis, the risk of ICU readmission was found to be independently associated with late group (HR, 1.28; 95% CI, 1.13-1.47).

**Conclusions:** Early post-discharge cardiopulmonary rehabilitation among ICU survivors has the long-term survival benefit and significantly decreases the readmission rate.

**Keywords:** Intensive care unit, early cardiopulmonary rehabilitation, mortality, readmission

## Introduction

Intensive care unit (ICU) is an important place for resuscitation and saving life of critically ill patients. However, the process of critical care during ICU stay may also bring several complications, such as nosocomial infections, ventilator-associated lung injury, adverse drug effects, venous thromboembolism, delirium, and stress ulcers related gastrointestinal tract bleeding.<sup>1-3</sup> Even for the patients with survive after ICU discharges, some of patients may be left with exercise limitation, physical disability, psychological dysfunction, and decreased physical quality of life for a long time.<sup>4-7</sup> Moreover, these functional disabilities and impairment of physical performance due to muscle wasting and sarcopenia are associated with mortality.<sup>8-11</sup>

To decrease the negative impact of muscle wasting and functional disability after ICU discharge, rehabilitation may be a resolution for this clinical problem. For stroke patients, cardiorespiratory and mixed training, involving walking, within post-stroke rehabilitation programs was demonstrated to improve the functional activity.<sup>12</sup> For patients with chronic obstructive pulmonary disease, supervised exercise programs after primary pulmonary rehabilitation is more effective than usual care for preserving exercise capacity than usual care.<sup>13</sup> For the patients receiving coronary artery bypass graft surgery, 10-year all-cause mortality can be reduced after cardiac rehabilitation.<sup>14</sup> For ICU survivors of sepsis, the long term outcome can be improved by post-discharge rehabilitation.<sup>15</sup> For critically ill patients in ICU, inpatients Physical therapy can improve the short-term outcomes – including improving quality of life, physical function, enhancing muscle strength, increasing decreasing ventilator-free days, and decreasing length of stay in ICU and hospital.<sup>16</sup> However, the appropriate timing of introducing rehabilitation program for ICU patients remains unclear.

Most of studies focus on the early rehabilitation for the critically ill patients during ICU stay, and the effect seems to be controversy.<sup>17-19</sup> In this study, we hypothesises that the ICU survivor would be in a relative stable status and cardiopulmonary rehabilitation in the early stage after ICU discharge may provide some benefit. Thus, this study is conducted to compare the effect of early and late post-discharge cardiopulmonary rehabilitation on the outcomes of ICU survivors.

## **Methods**

### **Data source**

The retrospective, cohort study used a sub-database of the Taiwan National Health Insurance Research Database (NHIRD) that contains information of all patients had ICU admission between 2000 and 2012. Detailed information including outpatient and inpatient medical care, diagnoses, surgical procedures, and prescribed medications for each insured patient was obtained, including diagnostic codes according to the clinical modification of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code. The study was approved by the Institutional Review Board (IRB) at Chi Mei Medical Center. The data used in this study are de-identified, and released to the public for research purposes; therefore, the IRB waived informed consent from the enrolled patients (IRB no: 10707-E01).

### **Patient selection**

Throughout the study period, a total of 49,185 patients with ICU admission ever received cardiopulmonary rehabilitation. If patients had multiple ICU admissions, we only enrolled the first time ICU admission. Overall, there were 2,136 patients received rehabilitation of cardiopulmonary training after ICU

discharge. The cardiopulmonary rehabilitation was identified from the claiming medical expenditure claim applications. Among them, 994 patients had received cardiopulmonary rehabilitation within 30 days after ICU discharge, and were classified as early group. Another 1,142 patients had received cardiopulmonary rehabilitation between 30 days and one year after ICU discharge, and were classified as late group (figure 1). **Baseline variables and**

### **outcome measurement**

Demographic and clinical characteristics, including age, gender, comorbidities, and Charlson's Comorbidity Index (CCI) score, length of ICU stay were collected. The comorbidities, including of chronic obstructive pulmonary diseases (COPD; ICD-9-CM: 490-496), diabetes mellitus (DM; ICD-9-CM: 250), dementia (ICD-9-CM: 290, 294, 331), congestive heart failure (ICD-9-CM: 428), cerebrovascular disease (ICD-9-CM: 430-438), myocardial infarction (ICD-9-CM: 410-412), and malignancy (ICD-9-CM: 140-208), was defined as the records from one-year before the date of ICU admission. The end points were mortality and re-admission during the 3-year follow-up.

### **Statistical analysis**

The baseline characteristics, including age, gender, comorbidities, group of CCI score, length of ICU stay, and outcomes (mortality and ICU readmission), are presented as frequency with percentage, and the differences between early and late cardiopulmonary rehabilitation were evaluated using Pearson's  $\chi^2$  test for these categorical variables. Kaplan-Meier curves were used to plot the cumulative incidence rates of mortality and ICU readmission among study subjects, and a log-rank test was used to compare the risk differences between early and late cardiopulmonary rehabilitation. In addition, the relative risk ratio of mortality and ICU readmission between the patients receiving

cardiopulmonary training rehabilitation post-ICU discharge within 30 days and more than 30 days within one-year during the follow-up period was estimated using Cox proportional hazard regression. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Significance was set at  $P < 0.05$  (two-sided). Kaplan-Meier curves were plotted using Stata 12 (Stata Corp., College Station, TX, USA).

## Results

### Comparison between early and late rehabilitation groups

Among 2136 patients received cardiopulmonary rehabilitation after ICU discharge, 994 received early rehabilitation within 30 days after discharge, and other 1142 patients receive late rehabilitation between 30 days and one year after discharge (figure 1). Table 1 summarized their demographics and clinical characteristics. The distribution of age was different between early and late group ( $p = 0.0164$ ). Early group had less COPD, CHF, cerebrovascular disease, and malignancy than late group. In contrast, early group had more myocardial infarction than late group. Overall, early group had a lower mortality rate (6.64% vs 10.86%,  $p = 0.0006$ ), and a lower ICU readmission rate (47.8% vs 57.97%,  $p < 0.0001$ ) than late group. Late group had a longer length of ICU stay than early rehabilitation group ( $p < 0.0001$ ).

### Risk of mortality

Using univariate analysis, late group was associated with higher risk of mortality than early group (HR, 1.65, 95% CI, 1.22-2.22). Kaplan-Meier analysis showed that early group had a lower mortality rate than late rehabilitation ( $p = 0.0009$ ) (Figure 2). Patients older than 75 years had higher mortality than the patients younger than 30 years (HR, 6.22; 95% CI, 2.80-13.84). Patients with COPD,

DM, dementia, CHF, cerebrovascular and malignancy had higher risk of mortality than patients without underlying comorbidity (all  $p < 0.005$ ). Patients had CCI scores more than 2 had higher risk of mortality than the patients with CCI score of 0. Patients with length of ICU stay more than 15 days had higher risk of death than those with less than 15 days (HR, 2.27, 95% CI, 1.68-3.07). After multivariate analysis, the risk of mortality was found to be independently associated with old age ( $\geq 75$  years) (HR, 2.90; 95% CI, 1.25-6.74), malignancy (HR, 1.80; 95% CI, 1.07-3.06), and prolong ICU stay (more than 15 days) (HR, 1.60; 95% CI, 1.14-2.24).

### **Risk of ICU readmission**

Using univariate analysis, late group was associated with a higher risk of ICU readmission than early group (HR, 1.38, 95% CI, 1.22-1.55). Kaplan-Meier analysis showed that early rehabilitation group had a lower ICU readmission rate than late rehabilitation ( $p < 0.0001$ ) (Figure 3). Patients older than 60 years had a higher risk of ICU readmission than the patients younger than 30 years. Patients with COPD, DM, dementia, CHF, cerebrovascular, myocardial infraction, and malignancy had a higher risk of readmission than patients without underlying comorbidity (all  $p < 0.05$ ). Patients had CCI scores more than 2 had a higher risk of readmission than the patients with CCI score of 0. Patients with length of ICU stay more than 15 days had a higher risk of ICU readmission than those with less than 15 days (HR, 2.27, 95% CI, 1.68-3.07). After multivariate analysis, the risk of ICU readmission was found to be independently associated with late rehabilitation (HR, 1.28; 95% CI, 1.13-1.47), old age ( $\geq 75$  years) (HR, 1.68; 95% CI, 1.17-2.41), dementia (HR, 1.67; 95% CI, 1.19-2.34), cerebrovascular disease (HR, 1.26; 95% CI, 1.05-1.51), myocardial infraction (HR, 1.43, 95% CI, 1.25-1.65), and higher CCI scores ( $>$

4) (HR, 1.52; 95%, 1.13-2.04).



## Discussion

This study is the first population-based nationwide study to compare the effect of early and late post-discharge cardiopulmonary rehabilitation on the outcomes of ICU survivors. The results showed that early cardiopulmonary rehabilitation within 30 days post-discharge might decrease 3-year mortality and significantly decreased the readmission rate. Besides, the effect remained constant among some subgroups, as age >75 years, cancers co-morbidity and ICU stays >15 days had a survival benefit, and those whose age >75 years, co-morbidities of stroke and myocardial infarction and CCI >4 had a less hospital readmission. While the critically ill patients survive discharge from ICU, they should just begin recovering from the energy loss, muscle weakness, and physical inactivity.<sup>5,6</sup> Thus, rehabilitation should be important for these patients. In a randomized controlled trial, Jones et al showed rehabilitation after critical illness can help improve Short-Form Health Survey physical function scores at 8 weeks and 6 months ( $p = .006$ ).<sup>20</sup> Another study<sup>15</sup> showed that post-ICU discharge rehabilitation for the ICU survivor of sepsis was associated with a 5.6% risk reduction in mortality. In this study, we found that early rehabilitation for these patients can provide more outcome benefit than late rehabilitation, and it further expands our understanding of post-ICU discharge rehabilitation in terms of timing.

It is well known that patient compliance with post-discharge rehabilitation is lower than compliance in the ICU or other hospital wards, and early post-discharge rehabilitation may break this vicious cycle of functional disability and post-critical mortality by improving muscle strength and functional activity.<sup>21</sup> A recent systematic review and meta-analysis of hospital based inpatient geriatric rehabilitation, including exercise training, demonstrated that rehabilitation

strategies cannot only restore functioning but also prevent disabilities.<sup>22</sup> Within 12 months of hospital discharge, Davidson et al. reported elderly patients had lower hospital readmission rates in the rehabilitation group (relative risk: 0.63).<sup>23</sup> Besides, Chao et al. displayed that critical ill survivors aged between 60-80 years with post-discharge rehabilitation had a lower mortality.<sup>15</sup> Our study also showed age > 75 with early post-discharge rehabilitation had significantly lower mortality and readmission.

Clinical practice guidelines recommend rehabilitation evaluation and treatment as soon as possible after hospital admission.<sup>24</sup> Freburger et al. found that compared to those who received no therapy, individuals who received rehabilitation in the first 30 days after discharge home after stroke were less likely to be readmitted to the hospital in the subsequent 30 days.<sup>25</sup> The present study displayed that early post-discharge rehabilitation among ICU survivors with stroke could prevent further readmission.

Shannon et al described that 1569 Cardiac rehabilitation participants after hospital discharge had lower all-cause readmission (HR 0.75), cardiovascular readmission (HR 0.80), non-cardiovascular readmission (HR 0.72), and mortality (HR 0.58) risk, and most of them (>90%) received rehabilitation program within 30 days.<sup>26</sup> Our study also displayed early post-discharge rehabilitation could decrease readmission among patients with myocardial infarction.

As cancer survivorship is increasing, but physical, cognitive and emotional sequelae post life-saving treatments often leave people with activity and participation limitations. Hauken et al. displayed a rehabilitation program tailored for cancer patients seemed to build positive health outcomes and physical capacity in a long-term perspective.<sup>27</sup> Our study also evidenced a

survival benefit of early rehabilitation for critically ill survivors with cancer.

A study on rehabilitation cohort comprised 15,535 ICU sepsis survivors received post-discharge rehabilitation within 3 months showed that CCI >3, ICU stays  $\geq 7$  days and hospital stays  $\geq 21$  days significantly decreased the risk of mortality relative to the control cohort.<sup>15</sup> Our study also showed that early post-discharge rehabilitation had a significant mortality reduction among patients with ICU stay more than 15 days, and also had a lower readmission rate among those who had a CCI > 4.

Our findings can be explained by several mechanisms. First, cardiovascular and respiratory failures are the most common dysfunctional organs in ICUs; therefore, cardiopulmonary rehabilitation can help recovery of the patients just survived through the critical illness. Second, cardiopulmonary rehabilitation has been proven its effect in improving ventilator efficiency and VO<sub>2</sub> kinetics for patients with coronary artery disease,<sup>28</sup> in enhancing functional capacity, and quality of life for patients with heart failure,<sup>29</sup> in relieving dyspnea and improving exercise capacity for patients with chronic obstructive pulmonary diseases.<sup>30,31</sup> Third, the time frame of introducing rehabilitation is post-ICU discharge, not in the acute stage in the ICU. Thus, the concern about wasting patients' energy against the disease, increasing risk of rehabilitation associated side effect in the unstable conditions, frequent interruption of rehabilitation due to many examinations and treatment in the ICU,<sup>32</sup> may be minimized.

Our study has some strength. This is the first study with a 12-year nationwide cohort survey to investigate whether early post-discharge rehabilitation is associated with improved long-term survival and decreased hospital re-admission in ICU survivors. Additionally, this study has several limitations. First,

from the NHIRD database, we cannot obtain the data of patients' physical performance, muscle strength, functional status, and quality of life. We just can measure the definite and solid outcomes, such as all-cause mortality and readmission. Second, we cannot avoid selection bias. The implementation of rehabilitation program depends on the physicians' judgement and patient's clinical condition. Therefore, we did not try to compare the outcome of patients with or without rehabilitation. In addition, we choose the post-ICU discharge stage for study. In this study, these ICU survivors should recover from the acute stage and remain in a relative stable status. Thus, the effect of selection bias can be minimized. Third, this study is not randomized controlled trial, so we cannot perfectly match the each study group. However, our findings are based on the real world's situation, and can be generalized to other hospitals.

In conclusion, the present study showed that early post-discharge (within 30 days) rehabilitation among ICU survivors might have the long-term survival benefit and significantly decreases the readmission rate. Elderly, more co-morbidities (including cancer, stroke and myocardial infarction) and longer ICU stays may be a target subpopulation likely to benefit most from post-discharge rehabilitation.

## Legend

Figure 1. Flow chart of patient selection

Figure 2. Probability of survival rate among early and later rehabilitation group

Figure 3. Cumulative incidences of readmission among early and later rehabilitation group

Table1 Demographics and clinical characteristics of patients with rehabilitation after ICU discharge

	Received early rehabilitation (<30 days)	Received delayed rehabilitation (>30 days)	P-value
	N=994(46.54)	N=1142(53.46)	
Age group, years old			0.0164
18-35	40(4.02)	60(5.25)	
35-50	191(19.22)	179(15.67)	
50-65	397(39.94)	429(37.57)	
65-80	321(32.29)	396(34.66)	
More than 80	45(4.53)	78(6.83)	
Gender			0.5608
Female	239(24.04)	287(25.13)	
Male	755(75.96)	855(74.87)	
Comorbidities			
Chronic obstructive pulmonary disease	96(9.66)	176(15.41)	<0.0001
Diabetes mellitus	323(32.49)	362(31.70)	0.6941
Dementia	16(1.61)	30(2.63)	0.1062
Congestive heart failure	194(19.52)	297(26.01)	0.0004
Cerebrovascular disease	92(9.26)	181(15.85)	<0.0001
Myocardial infarction	395(39.74)	307(26.88)	<0.0001
Malignancy	24(2.41)	66(5.78)	0.0001
CCI group			<0.0001
0	166(16.70)	185(16.20)	
1	416(41.85)	372(32.57)	
2	211(21.23)	257(22.50)	
More than 2	201(20.22)	328(28.72)	
ICU stay, days			<0.0001
<15	738(74.25)	392(34.33)	
More than 15	256(25.75)	750(65.67)	
Outcome			
Death	66(6.64)	124(10.86)	0.0006
Re-admission	471(47.38)	662(57.97)	<0.0001

P-value was derived from Pearson's chi-square test for categorical variables and T-test for continuous variables.

Table 2. Risk factor of 3-year mortality in patients with rehabilitation after ICU discharge.

	Univariate HR (95% C.I.)	P-value	Multivariate HR (95% C.I.)	P-value
Comparison				
Early PTC5 after discharge	Ref.		Ref.	
Delayed PTC5 after discharge	1.65(1.22-2.22)	0.0011	1.05(0.76-1.47)	0.7575
Age group, years old				
18-30	Ref.		Ref.	
30-44	0.74(0.31-1.78)	0.5051	0.66(0.27-1.59)	0.3520
45-59	0.83(0.38-1.84)	0.6466	0.57(0.25-1.30)	0.1843
60-74	1.57(0.72-3.40)	0.2546	0.90(0.40-2.00)	0.8046
More than 75	6.22(2.80-13.84)	<.0001	2.90(1.25-6.74)	0.0132
Gender				
Female	Ref.		Ref.	
Male	1.20(0.85-1.69)	0.2990	1.30(0.91-1.84)	0.1439
Comorbidities				
Chronic obstructive pulmonary disease	2.63(1.91-3.61)	<.0001	1.367(0.95-1.98)	0.0971
Diabetes mellitus	1.47(1.10-1.97)	0.0089	1.27(0.89-1.81)	0.1893
Dementia	3.33(1.85-5.97)	<.0001	1.52(0.82-2.80)	0.1806
Congestive heart failure	1.65(1.22-2.24)	0.0012	1.17(0.84-1.64)	0.3458
Cerebrovascular disease	1.92(1.37-2.71)	0.0002	1.18(0.80-1.74)	0.4057
Myocardial infarction	0.82(0.60-1.13)	0.2215	0.90(0.64-1.27)	0.5571
Malignancy	3.03(1.93-4.78)	<.0001	1.801(1.07-3.06)	0.0277
CCI group				
0	Ref.		Ref.	
1	1.25(0.69-2.25)	0.4691	1.17(0.63-2.17)	0.6277
2-4	2.59(1.45-4.63)	0.0013	1.75(0.89-3.43)	0.1045
More than 4	4.14(2.40-7.17)	<.0001	1.92(0.91-4.04)	0.085
ICU stay, days				
<15	Ref.		Ref.	

More than 15	2.27(1.68-3.07)	<.0001	1.60(1.14-2.24)	0.0065
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Table 3. Risk factor of readmission in patients with rehabilitation after ICU discharge

	Univariate HR (95% C.I.)	P-value	Multivariate HR (95% C.I.)	P-value
Comparison				
Early PTC5 after discharge	Ref.		Ref.	
Delayed PTC5 after discharge	1.38(1.22-1.55)	<.0001	1.28(1.13-1.47)	0.0002
Age group, years old				
18-30	Ref.		Ref.	
30-44	0.84(0.61-1.16)	0.2869	0.75(0.54-1.05)	0.0920
45-59	0.97(0.72-1.31)	0.8332	0.79(0.58-1.07)	0.1292
60-74	1.43(1.06-1.93)	0.0181	1.07(0.78-1.46)	0.6791
More than 75	2.30(1.62-3.25)	<.0001	1.68(1.17-2.41)	0.0049
Gender				
Female	Ref.		Ref.	
Male	1.01(0.88-1.15)	0.9361	1.01(0.88-1.15)	0.9874
Comorbidities				
Chronic obstructive pulmonary disease	1.31(1.12-1.55)	0.0011	1.00(0.83-1.20)	0.9707
Diabetes mellitus	1.34(1.19-1.52)	<.0001	1.10(0.94-1.29)	0.227
Dementia	2.60(1.88-3.59)	<.0001	1.67(1.19-2.34)	0.0029
Congestive heart failure	1.16(1.01-1.33)	0.0347	1.07(0.912-1.24)	0.4096
Cerebrovascular disease	1.71(1.46-1.99)	<.0001	1.26(1.05-1.51)	0.0126
Myocardial infarction	1.34(1.19-1.51)	<.0001	1.43(1.25-1.65)	<.0001
Malignancy	1.74(1.36-2.24)	<.0001	1.23(0.92-1.63)	0.1625
CCI group				
0	Ref.		Ref.	
1	1.21(1.00-1.47)	0.0537	1.03(0.84-1.28)	0.7544
2-4	1.66(1.35-2.03)	<.0001	1.17(0.91-1.52)	0.2270
More than 4	2.43(2.00-2.94)	<.0001	1.52(1.13-2.04)	0.0052
ICU stay, days				
<15	Ref.		Ref.	



More than 15	1.28(1.14-1.44)	<.0001	1.04(0.91-1.19)	0.5235
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Figure 1. Flow chart of patient selection

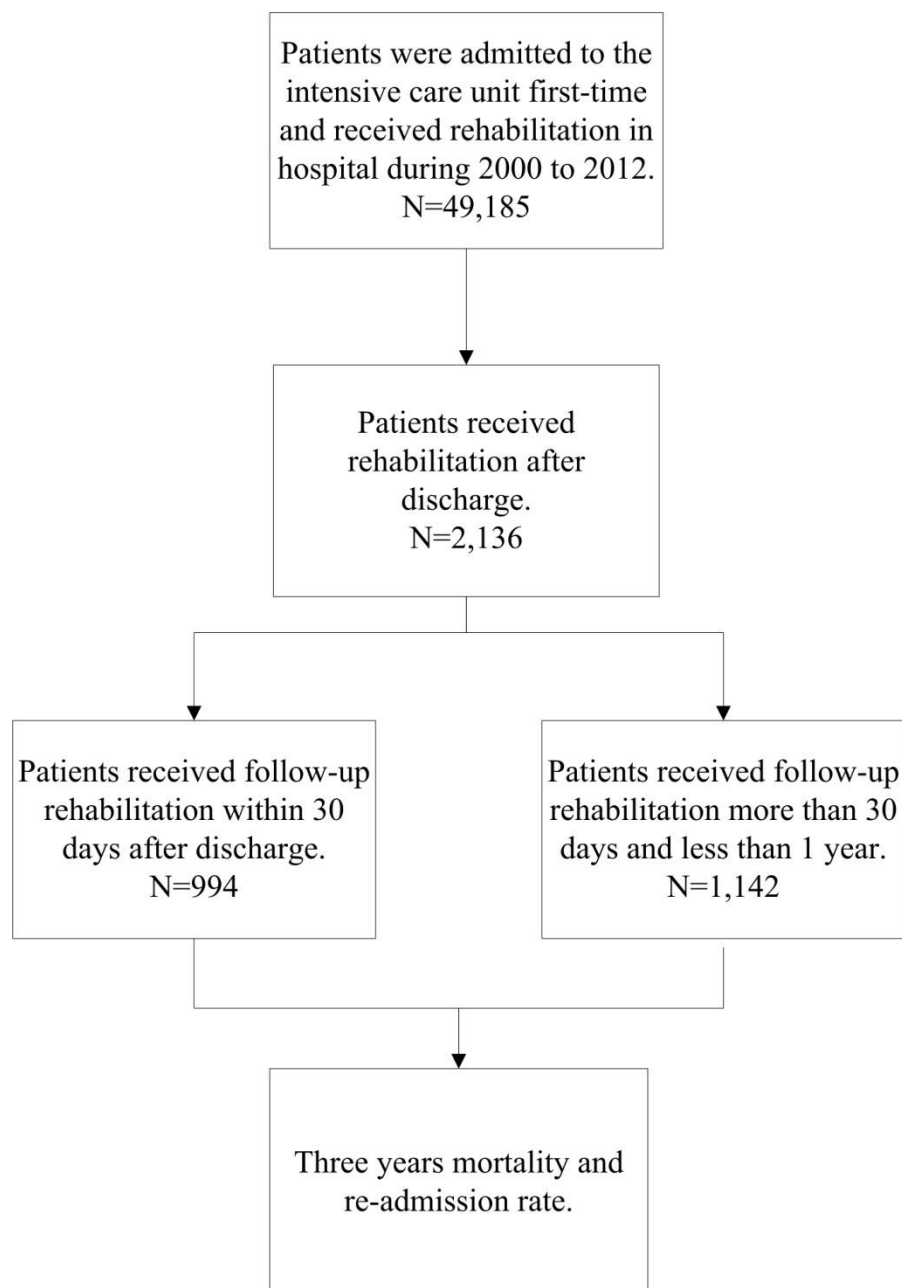


Figure 2. Probability of survival rate among early and later rehabilitation group

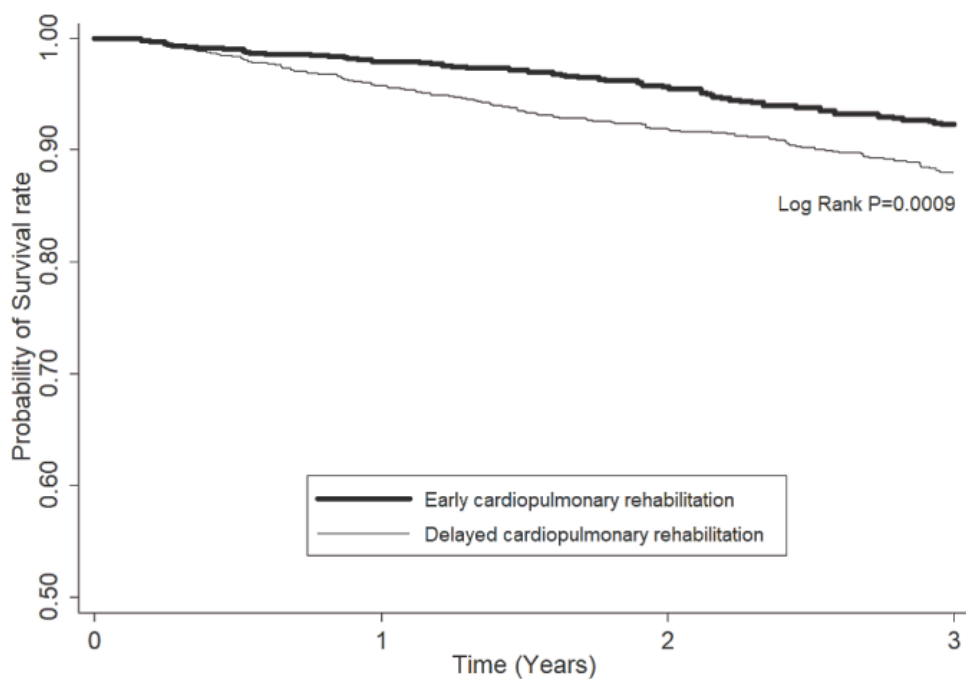
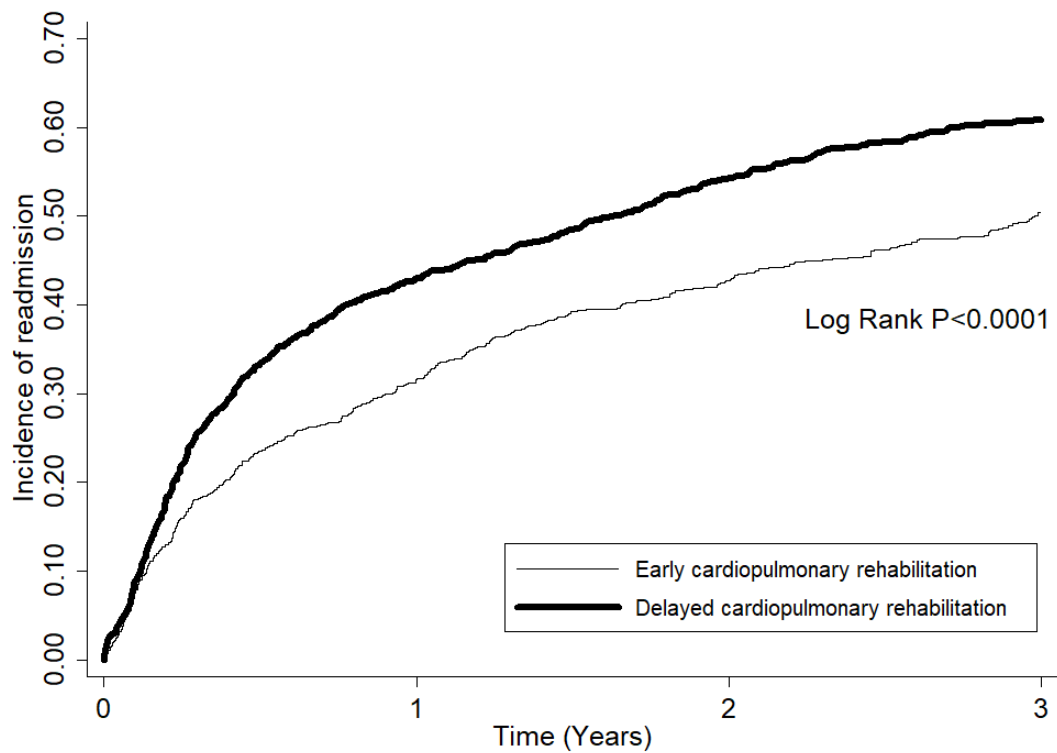


Figure 3. Cumulative incidences of readmission among early and later rehabilitation

group



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