Effect of Alzheimer Disease on Prognosis of Intensive Care Unit (ICU) Patients: A Propensity Score Matching Analysis

**Background:** The growing number of patients with Alzheimer disease worldwide has become a leading public concern. Whether Alzheimer disease has an impact on the outcomes of critically ill patients remains unclear; therefore, we conducted this study to evaluate comorbid Alzheimer disease in patients in the Intensive Care Unit (ICU).

**Material/Methods:** Data were extracted from the Medical Information Mart for Intensive Care-III database, version 1.4. Patients were divided into an Alzheimer disease group and a non-Alzheimer disease group. Differences in all-cause mortality, length of hospital stay, mechanical ventilation rate, and mechanical ventilation duration were analyzed. Propensity score matching (PSM) was performed to compensate for differences in baseline characteristics. The differences in prognosis were compared between groups after PSM. Survival analyses in patients were performed and Cox regression analyses were used to predict prognoses.

**Results:** We included 33 935 patients, among which 433 patients were comorbid with Alzheimer disease. After PSM, there were no significant differences in 7-day mortality, but there were significant differences in 28-day mortality ($P=0.047$) and 90-day mortality ($P=0.012$) between the 2 groups. There was also a significant difference in the 4-year cumulative survival between the 2 groups ($P<0.001$). In all patients undergoing surgery, multivariate Cox regression analysis showed that Alzheimer disease comorbidity was significantly associated with 90-day mortality and 4-year mortality.

**Conclusions:** Critical ill patients with Alzheimer disease had higher 28-day and 90-day mortality. Especially for patients undergoing surgery, Alzheimer disease is an independent risk factor affecting long-term survival.

**Keywords:** Alzheimer Disease • Intensive Care Units • Mortality • Propensity Score

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Background

Dementia is a prevalent progressive neurodegenerative disease that causes impaired memory, reasoning, and cognitive functions [1]. From 1990 to 2016, the number of dementia-related deaths climbed by 148% globally. After ischemic heart disease, chronic obstructive pulmonary disease, intracerebral hemorrhage, and ischemic stroke, dementia was the fifth leading cause of death (2.4 million deaths) globally in 2016 [2]. Alzheimer disease (AD) is the most common type of dementia and the leading cause of disability in elderly people. By 2050, 13.8 million older persons in the United States are expected to have cognitive impairment due to Alzheimer disease and related dementias (ADRD) [3,4]. In future decades, as the world’s population ages, Alzheimer disease is projected to become a significant burden for families and society [5]. It will present profound challenges to patients, families, healthcare institutions, and society all over the world [6]. It is one of the most critical and challenging public health threats of the twenty-first century [7]. Higher-morbidity falls, urinary tract infections (UTI), and overall hospitalization are all associated with Alzheimer’s disease [8]. The direct cause of these adverse outcomes is almost always a loss of cognitive performance and function [9,10], rather than an increase in brain lesions. Numerous and varied attempts have been made to develop a disease-modifying approach, but none have shown clinical benefits in patients due to the complex pathological mechanism of AD [11]. Even in August 2018, France’s health insurance system refused to pay for 4 medications for AD (donepezil, lisdexamfetamine, galantamine, and memantine hydrochloride) due to lack of efficacy and a variety of adverse effects [12]. The vulnerability of ADRD patients is magnified by the morbidity and mortality of COVID-19, as well as the indirect impact of the pandemic on social support and health care systems [13]. As a result, it is critical to determine how AD affects the prognosis of patients in the intensive care unit (ICU) as soon possible. However, there is limited evidence that co-morbid AD has any impact on critically ill individuals. In this study, our purpose was to evaluate whether there is a relationship between the presence or absence of AD comorbidity and the prognoses of critically ill ICU patients and whether surgical treatments are associated with this.

Material and Methods

Data Sources

Data were exacted from the Medical Information Mart for Intensive Care (MIMIC)-III database version 1.4, which is a large, publicly and freely available dataset composed of patients admitted to the Beth Israel Deaconess Medical Center ICU (BIDMC, Boston, MA) between 2001 and 2012 [14]. The use of the MIMIC-III database was approved by the Institutional Review Boards of BIDMC and the Massachusetts Institute of Technology (certification number: 36300529). Because all data were deidentified, individual informed consent was not required. The clinical and laboratory data of critically ill patients were extracted from the MIMIC-III database using structured query language (SQL).

Inclusion and Exclusion Criteria

Patients older than age 18 years staying in the ICU for more than 24 h were included. For patients with multiple ICU admissions, only the first stay was analyzed. Data were filtered using the following exclusion criteria: 1) age <18 years, 2) ICU stay <24 h, 3) repeated hospitalizations, 4) missing data (no data on ICU discharge). All included patients were divided into 2 groups: AD and non-AD.

The diagnosis of AD was identified in the present study based on the ICD-9 code ‘3310’.

Definitions and Outcomes

The primary study endpoint was all-cause mortality after ICU admission (7-day mortality, 28-day mortality, 90-day mortality, and 4-year overall survival). Secondary outcomes included: hospital length of stay after ICU admission (Hos LOS), ICU length of stay (ICU LOS), mechanical ventilation rate, and mechanical ventilation duration (Vent duration).

Propensity Score Matching

The propensity score (PS), first introduced by Rosenbaum and Rubin [15], is widely used to combine the information of the observed variables to balance the variables and reduce bias. Propensity score matching (PSM) is one of the propensity score methods used to mimic some of the characteristics of a randomized controlled trial [16]. Our unique analysis involved propensity score matching [17,18] to balance confounders between the 2 groups. In detail, the following baseline characteristics were used to generate the propensity score: age, sex, weight, congestive heart failure, hypertension, chronic pulmonary, chronic kidney disease, liver disease, diabetes, APS III, SOFA, and heart rate (HR). PSM was conducted using a 1:1 matching ratio with the nearest neighbor and sampling without replacement with a caliper of 0.05.

Statistical Analysis

Continuous variables with normal distribution are expressed as mean±standard deviation (SD); while other continuous variables with non-normal distribution are reported as median (interquartile range). Categorical variables are presented...
as frequencies and/or percentages. The between-group differences were compared using analysis of variance (ANOVA). The Wilcoxon rank sum test or Kruskal-Wallis test was performed, as appropriate. Survival curves were calculated according to the Kaplan-Meier method and survival analyses were performed by the log-rank test.

Univariate and multivariate Cox regression analyses were used with the Cox proportional hazards regression model to identify independent risk factors affecting prognosis.

All statistical analyses were performed using SPSS 25.0 software for Windows (SPSS Statistics Version 25.0, IBM Corp.). All statistical significance tests were two-sided and differences were considered statistically significant at $P$ value below 0.05.

**Results**

Initially, 61 532 records were identified from the MIMIC-III database, of which 27 597 were excluded (3996 were patients younger than 18 years, 11 685 had a stay of less than 24 h, 11 914 were repeated hospitalizations, and 2 patients had no information on the time of ICU discharge). In total, 33 935 patients were finally enrolled, of whom 433 had a diagnosis of AD (Figure 1). The mean age was 64.22±17.27 years, 19 269 patients (56.78%) were male, and the average body weight was 81.05±23.86 kg.

There were significant differences in age, sex, and comorbidity such as hypertension and congestive heart failure between the 2 groups (Table 1). Meanwhile, significant differences were noted in terms of 7-day, 28-day, and 90-day mortality, hospital and ICU length of stay, and mechanical ventilation rate (Table 2).

To balance the distribution of baseline characteristics, we used propensity score matching (PSM). After matching, there were 405 patients in each group. No significant differences in baseline characteristics were detected between the 2 groups ($P>0.05$) (Table 3). Significant differences were observed in 28- and 90-day mortality and mechanical ventilation rate between groups (Table 4). In addition, we performed a statistical analysis of the diagnosis of these 2 groups of patients admitted to the ICU, as detailed in Supplementary Table 1.

A four-year survival analysis showed significant differences between the AD group and non-AD group (34.2% and 65.1%, respectively, $P<0.001$) (Figure 2). We further analyzed all patients in the ICU who underwent surgery (excluding patients with surgical diseases who preferred nonsurgical treatment). We found a significant difference between the surgical patients with AD and surgical patients without AD in the 4-year survival analysis ($P<0.001$) (Figure 3). Univariate and multivariate Cox regression analyses were performed to determine predictive factors for outcomes of those surgical patients in the ICU. AD comorbidity was significantly associated with 90-day survival (hazard ratio: 1.888, $P=0.003$) and 4-year survival (hazard ratio: 1.839, $P<0.001$) (Tables 5, 6).

**Discussion**

There were 3 main findings of our study. First, all-cause mortality at 28 and 90 days in the AD group was significantly higher than in the non-AD group, and this significance remained even after PSM. In addition, in critically ill patients undergoing surgery, we found AD to be an independent risk factor predicting poor outcomes. Last but not least, there were no differences in the duration of ICU treatment, length of stay, and duration of mechanical ventilation between the AD and non-AD groups after PSM.

In 1907, the German psychiatrist Alois Alzheimer published a case report of a 51-year-old woman who had died of dementia and whose brain showed plaques and tangles. Emil Kraepelin, the leading German psychiatrist, singled out “Alzheimer’s disease” as “a more or less age-independent unique disease process” in 1910 [19]. The World Health Organization defines AD as a degenerative brain disease of unknown etiology with typical neuropathological and neurochemical characteristics [20].
### Table 1. Demographical characteristics and clinical basis data of the patients.

| Variables               | All patients (n=33935) | Non-AD group (n=33502) | AD group (n=433) | P value |
|-------------------------|------------------------|------------------------|------------------|---------|
| Demographics            |                        |                        |                  |         |
| Age (y, Mean±SD)        | 64.22±17.27            | 63.98±17.23            | 82.59±6.28       | <0.000  |
| Gender (% Male)         | 19269 (56.78%)         | 19087 (57%)            | 182 (42%)        | 0.000   |
| Weight (kg)             | 81.05±23.86            | 81.21±23.9             | 68.66±16.31      | >0.000  |
| Comorbidity (%)         |                        |                        |                  |         |
| Congestive heart failure| 4614 (13.6%)           | 4524 (13.5%)           | 90 (20.8%)       | 0.000   |
| Valvular disease        | 1651 (4.9%)            | 1620 (4.8%)            | 31 (7.2%)        | 0.026   |
| Peripheral vascular     | 2877 (8.5%)            | 2846 (8.5%)            | 31 (7.2%)        | 0.321   |
| Hypertension            | 3253 (9.4%)            | 3125 (9.3%)            | 71 (16.4%)       | 0.000   |
| Congestive heart failure| 6603 (17.7%)           | 5937 (17.7%)           | 66 (15.2%)       | 0.179   |
| Valvular disease        | 1964 (5.8%)            | 1956 (5.8%)            | 8 (1.8%)         | 0.000   |
| Peripheral vascular     | 2877 (8.5%)            | 2846 (8.5%)            | 31 (7.2%)        | 0.321   |
| Hypertension            | 3253 (9.4%)            | 3125 (9.3%)            | 71 (16.4%)       | 0.000   |
| Chronic pulmonary       | 6003 (17.7%)           | 5937 (17.7%)           | 66 (15.2%)       | 0.179   |
| Diabetes                | 8535 (26.6%)           | 8428 (25.2%)           | 107 (24.7%)      | 0.832   |
| Hypothyroidism          | 3196 (9.4%)            | 3125 (9.3%)            | 71 (16.4%)       | 0.000   |
| Chronic kidney disease  | 3902 (11.5%)           | 3832 (11.4%)           | 70 (16.2%)       | 0.002   |
| Liver disease           | 1964 (5.8%)            | 1956 (5.8%)            | 8 (1.8%)         | 0.000   |
| Lymphoma                | 419 (1.2%)             | 414 (1.2%)             | 5 (1.2%)         | 0.879   |
| Rheumatoid arthritis    | 887 (2.6%)             | 868 (2.6%)             | 19 (4.4%)        | 0.020   |
| Surgery                 | 10916 (32.2%)          | 10845 (32.4%)          | 71 (16.4%)       | 0.000   |
| Treatment               |                        |                        |                  |         |
| Vasopressor             | 12753 (37.6%)          | 12641 (37.7%)          | 112 (25.9%)      | <0.000  |
| RRT                     | 674 (1.99%)            | 672 (2.0%)             | 2 (0.5%)         | 0.022   |
| Score                   |                        |                        |                  |         |
| SOFA (4)                | 2295 (6.8%)            | 2253 (6.7%)            | 42 (9.7%)        | 0.014   |
| APS III (39)            | 29 (29, 52)            | 29 (29, 52)            | 45 (36.5, 59)    | <0.000  |
| SAPS II (33)            | 25 (25, 43)            | 25 (25, 43)            | 42 (36, 50)      | 0.000   |
| GCS (14)                | 25 (15)                | 25 (15)                | 11 (8, 14)       | 0.000   |
| HR (bpm)                | 85.07±18.4             | 85.1±18.4              | 82.54±17.5       | 0.663   |

Data presented as n (%), mean±SD, or median and interquartile range (IQR). P values are comparisons between Alzheimer’s disease group with non-Alzheimer’s disease group. * Means uneven variance using F test. RRT – renal replacement therapy; SOFA – Sequential Organ Failure Assessment; APS III – Acute Physiology Score III; SAPS II – Simplified Acute Physiology Score II; GCS – Glasgow Coma Score; HR – heart rate.

### Table 2. Outcomes of the patients.

| Variables               | All patients (n=33935) | Non-AD group (n=33502) | AD group (n=433) | P-value |
|-------------------------|------------------------|------------------------|------------------|---------|
| Mortality rates (%)     |                        |                        |                  |         |
| 7-day mortality         | 2415 (6.9%)            | 2352 (6.9%)            | 63 (14.6%)       | <0.000  |
| 28-day mortality        | 4454 (13.1%)           | 4351 (13%)             | 103 (23.8%)      | 0.000   |
| 90-day mortality        | 6161 (18.2%)           | 6008 (17.9%)           | 153 (35.3%)      | 0.000   |
| ICU LOS(h)              | 110.7±151.5            | 110.7±151.9            | 97.8±112.5       | <0.019  |
| Hos LOS(d)              | 9.6±10.0               | 9.6±10.1               | 8.57±6.68        | <0.002  |
| Mechanical ventilation  | 18302 (53.9%)          | 18121 (54.1%)          | 181 (41.8%)      | 0.000   |
| Vent durations(h)       | 31.6±80.9              | 31.6±80.9              | 32.39±78.3       | 0.841   |

LOS – length of stay. * Means uneven variance using F test.
### Table 3. Demographic characteristics and clinical data of the patients after PSM.

| Variables                  | AD group (n=405) | Non-AD group (n=405) | P value |
|----------------------------|------------------|----------------------|---------|
| Demographics               |                  |                      |         |
| Age (y, Mean ± SD)         | 82.78±7.96       | 82.16±8.34           | 0.631   |
| Gender (% Male)            | 173 (42.7%)      | 11 (2.7%)            | 0.023   |
| Weight (kg)                | 67.41±15.88      | 69.42±16.26          | 0.654   |
| Comorbidity (%)            |                  |                      |         |
| Congestive heart failure   | 71 (17.5%)       | 85 (21.0%)           | 0.212   |
| Valvular disease           | 23 (5.7%)        | 28 (6.9%)            | 0.470   |
| Peripheral vascular        | 44 (10.9%)       | 30 (7.4%)            | 0.088   |
| Hypertension               | 40 (9.9%)        | 58 (14.3%)           | 0.052   |
| Chronic pulmonary diabetes | 50 (12.3%)       | 63 (15.6%)           | 0.187   |
| Chronic kidney disease     | 49 (12.1%)       | 65 (16.0%)           | 0.106   |
| Liver disease              | 4 (1.0%)         | 9 (2.0%)             | 0.245   |
| Lymphoma                   | 9 (2.2%)         | 5 (1.2%)             | 0.281   |
| Tumor                      | 7 (1.7%)         | 11 (2.7%)            | 0.680   |
| Rheumatoid arthritis       | 14 (3.5%)        | 17 (4.2%)            | 0.583   |
| Treatment                  |                  |                      |         |
| Vasopressor                | 134 (33.1%)      | 111 (27.4%)          | 0.079   |
| RRT                        | 5 (1.2%)         | 2 (0.5%)             | 0.451*  |
| Score                      |                  |                      |         |
| SOFA                       | 4 (2.6)          | 4 (2.6)              | 0.267   |
| APS III                    | 42 (33.57)       | 45 (36.58)           | 0.095   |
| GCS                        | 11 (5.14)        | 11 (8.14)            | 0.320   |
| HR (bpm)                   | 82.39±17.7       | 82.56±17.7           | 0.610   |

Matching variables: Age, Sex, Weight, Congestive heart failure, Hypertension, Chronic pulmonary, Chronic kidney disease, Liver disease, Diabetes, APS III, SOFA, HR. Matching tolerance: 0.05.

Table 4. Outcomes of the patients after PSM.

| Variables                  | Non-AD group (n=405) | AD group (n=405) | P-value |
|----------------------------|----------------------|------------------|---------|
| Mortality rates (%)        |                      |                  |         |
| 7-day mortality            | 41 (10.1%)           | 11 (2.7%)        | 0.014   |
| 28-day mortality           | 73 (18.0%)           | 96 (23.7%)       | 0.047   |
| 90-day mortality           | 108 (26.7%)          | 141 (34.8%)      | 0.012   |
| ICU LOS(h)                 | 106.98±134.6         | 97.02±112.8      | 0.54    |
| Hos LOS(d)                 | 8.84±7.29            | 8.57±6.8         | 0.359   |
| Mechanical ventilation (%) | 215 (53.1%)          | 167 (41.2%)      | 0.001   |
| Vent durations(h)          | 27.99±66.84          | 31.62±78.17      | 0.143   |

LOS – length of stay.
Amyloid plaques, amyloid angiopathy, and neurofibrillary tangles have become hallmarks of Alzheimer disease [21]. Therefore, pathology examination remains the criterion standard for final diagnosis [22].

Previously, Alzheimer disease could only be definitively diagnosed post-mortem, but with improved diagnostic techniques and criteria, early diagnosis has become possible and challenging [23]. Magnetic resonance imaging and PET make it possible to effectively predict the progression of AD [19]. During this global pandemic, several characteristics of ADRD can increase

Table 5. Associations with 90-day mortality in critically ill patients who underwent surgery.

| Variables                      | Unadjusted (n: 10916) | Adjusted (n: 10916) |
|--------------------------------|-----------------------|---------------------|
|                                | HR (95% CI)           | P value             | HR (95% CI)          | P value          |
| Age                            | 1.038 (1.033, 1.042)  | 0.000               | 1.024 (1.020, 1.029) | 0.000            |
| Gender                         | 0.751 (0.668, 0.845)  | 0.000               |                      |                  |
| Weight                         | 0.985 (0.982, 0.988)  | 0.000               |                      |                  |
| Congestive heart failure       | 3.616 (3.105, 4.210)  | 0.000               | 2.399 (2.046, 2.813) | 0.000            |
| Hypertension                   | 1.863 (1.548, 2.241)  | 0.000               |                      |                  |
| Chronic pulmonary              | 1.364 (1.178, 1.579)  | 0.000               | 1.168 (1.007, 1.354) | 0.040            |
| Diabetes                       | 0.887 (0.771, 1.020)  | 0.092               |                      |                  |
| Hypothyroidism                 | 0.919 (0.738, 1.144)  | 0.449               |                      |                  |
| Chronic kidney disease         | 1.850 (1.553, 2.204)  | 0.000               |                      |                  |
| SOFA                           | 1.167 (1.147, 1.187)  | 0.000               |                      |                  |
| APS III                        | 1.031 (1.029, 1.034)  | 0.000               | 1.025 (1.022, 1.028) | 0.000            |
| GCS                            | 0.913 (0.902, 0.924)  | 0.000               | 0.957 (0.944, 0.971) | 0.000            |
| Alzheimer                      | 3.532 (2.337, 5.338)  | 0.000               | 1.890 (1.246, 2.867) | 0.003            |

SOFA – Sequential Organ Failure Assessment, APS III – Acute Physiology Score III; GCS – Glasgow Coma Score; HR – hazard ratio; CI – confidence interval.
the risk of contracting COVID-19. Individuals with dementia are more likely to have cardiovascular disease, diabetes, and pneumonia compared to individuals of the same age without dementia [24]. These conditions have been associated with poorer outcomes, including death [25].

In the current study, we have observed a significant difference in morbidity and mortality rates (at 28 days and 90 days) between the AD and non-AD groups in critically ill patients after PSM matching, and further survival analysis (90 days and 4 years) showed a significant difference. Our results suggest that AD does have a significant impact on both immediate and long-term survival of critically ill patients. This is in accordance with the conclusion of Brown et al [3,13]. Our data analysis demonstrated that comorbidity with AD means higher mortality in those critically ill individuals who need surgical treatments. Because AD patients have cognitive impairments and lack the ability to understand and cooperate with medical services, this requires critical care providers to pay more attention to these populations.

To date, effective drugs against AD are not available, and individuals with ADRD are depending on family or professional caregivers for their day-to-day survival [13,26], but the COVID-19 pandemic has had a dramatic impact on long-term care facilities, where the rates of infection and mortality have been very high. Community-based measures to slow the spread of the virus have forced social alienation and eliminated cognitive stimulation programs [27]. Therefore, a full understanding of the impact of AD on long-term prognosis would be more helpful in determining which therapeutic actions would be more beneficial for such patients. In our further analysis, we found that AD has an impact on intermediate survival (90-day, \( P<0.001 \)) and long-term (4-year, \( P<0.001 \)) survival in critically ill surgery patients. Multivariate Cox regression model analysis revealed that AD comorbidity was an independent risk factor influencing long-term survival (HR: 1.839, \( P<0.001 \)). Similar to the findings of studies of older patients on hemodialysis, we found that there is higher mortality associated with diagnoses of dementia and Alzheimer disease [28]. Due to the COVID-19 pandemic, if a successful cycle of vaccination is completed, long-term care plans for such patients should be restarted as soon as possible.

In secondary endpoint analysis, we found that combined AD did not have an impact on ICU and hospital length of stay or mechanical ventilation duration. In particular, the AD group showed a significantly lower mechanical ventilation rate than in the non-AD group, and no significant differences in mechanical ventilation duration were observed between the 2 groups.

We considered the possible reasons were as follows:

Unlike subcortical vascular dementia, episodic memory impairment (ie, amnesia, aphasia, and agnosia) is usually the earliest and most salient aspect of AD [21]. Importantly, AD patients are instead better able to accept and cooperate with treatment.

Table 6. Associations with 4-year mortality in critically ill patients who underwent surgery.

| Variables            | Unadjusted (n: 10916) | \( P \) value | Adjusted (n: 10916) | \( P \) value |
|----------------------|-----------------------|---------------|---------------------|--------------|
|                      | HR (95%CI)            |               | HR (95%CI)          |              |
| Age                  | 1.037 (1.034, 1.040)  | 0.000         | 1.027 (1.024, 1.030)| 0.000        |
| Gender               | 0.794 (0.734, 0.859)  | 0.000         | 0.993 (0.991, 0.996)| 0.000        |
| Weight               | 0.988 (0.986, 0.990)  | 0.000         | 2.302 (2.054, 2.581)| 0.000        |
| Congestive heart failure | 3.474 (3.116, 3.873)  | 0.000         |                     |              |
| Hypertension         | 1.834 (1.616, 2.081)  | 0.000         |                     |              |
| Chronic pulmonary    | 1.543 (1.403, 1.697)  | 0.000         | 1.327 (1.205, 1.460)| 0.000        |
| Diabetes             | 0.967 (0.883, 1.059)  | 0.472         |                     |              |
| Hypothyroidism       | 1.108 (0.968, 1.269)  | 0.135         |                     |              |
| Chronic kidney disease| 1.922 (1.709, 2.162)  | 0.000         | 1.218 (1.078, 1.377)| 0.002        |
| SOFA                 | 1.095 (1.081, 1.109)  | 0.000         | 0.974 (0.956, 0.992)| 0.005        |
| APS III              | 1.022 (1.020, 1.024)  | 0.000         | 1.020 (1.018, 1.023)| 0.000        |
| GCS                  | 0.960 (0.952, 0.968)  | 0.000         | 0.989 (0.979, 0.998)| 0.023        |
| Alzheimer            | 3.308 (2.439, 4.489)  | 0.000         | 1.839 (1.352, 2.501)| 0.000        |

SOFA – Sequential Organ Failure Assessment; APS III – Acute Physiology Score III; GCS – Glasgow Coma Score. HR – hazard ratio; CI – confidence interval.
Patients with AD often cannot take care of themselves, adhere to complex diets and medications, or be recognized as having new symptoms [28], which can be largely avoided during the ICU stay.

Based on the AD population’s relatively poor education and economic conditions, AD might not be the ‘real’ causal variant, but only a ‘proxy’ [29]. Therefore, the low rate of mechanical ventilation may be an artificial choice, which causes the comparison of mechanical ventilation duration to be worthless.

There are several limitations to this study. First, these retrospective comparisons with PSM were presented to minimize selection bias; however, some unobserved confounders may exist. For example, the diagnosis of AD is more dependent on advanced screening methods and advances in human knowledge of the disease, so there is a substantial degree of missing rates in early AD. Consequently, considering this specific target population, caution is needed in interpreting the results.

### Supplementary Material

**Supplementary Table 1.** The ICU admission diagnosis of these 2 groups after PSM.

| Variables (N%)          | AD group (n=405) | Non-AD group (n=405) |
|-------------------------|------------------|----------------------|
| Surgery                 | 69 (17%)         | 42 (10.4%)           |
| Tumor                   | 31 (7.7%)        | 14 (3.5%)            |
| Trauma                  | 16 (4%)          | 31 (7.7%)            |
| Neurological disease    | 24 (5.9%)        | 42 (10.4%)           |
| Respiratory disease     | 13 (3.2%)        | 19 (4.7%)            |
| Cardiovascular disease  | 175 (43.2%)      | 77 (19%)             |
| Digestive disease       | 27 (6.7%)        | 35 (8.6%)            |
| Infection               | 32 (7.9%)        | 92 (22.7%)           |
| Other disease           | 18 (4.4%)        | 53 (13.1%)           |

Data are presented as n (%). Other diseases are diseases not classified as above, such as psychiatric disorders, hematological diseases, alcohol abuse, and drug abuse.

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Meanwhile, due to the limitation of the database, the sample size is still small, and the representativeness of the data is not sufficient. A further multicenter prospective study with a larger cohort is necessary for further external validation.

### Conclusions

Critically ill patients with AD had a higher 28- and 90-day mortality and a worse 4-year survival rate. AD did not influence ICU length of stay, hospital length of stay, or duration of mechanical ventilation. AD was an independent risk factor for the long-term survival of critically ill patients who need surgery.

### Declaration of Figures’ Authenticity

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