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Original Article

Does the Timing of Depression Onset in Individuals with 2-Year Survival Coronary Artery Disease Affect Mortality? A Nationwide Retrospective Study

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SUMMARY

Background: Coronary artery disease (CAD) and depression often coexist, complicating disease management and worsening prognoses. Depression significantly increases mortality risk in CAD patients, but the impact of depression onset timing on long-term mortality in 2-year survival CAD patients remains unclear.
Methods: This retrospective cohort study used data from Taiwan's National Health Insurance Research Database from January 1, 2007, to December 31, 2014, including 1,254,084 individuals in the "no depression" group, 14,554 individuals in the "before CAD" group, 1,839 individuals in the "within one month" group, and 17,427 individuals in the "after one month" group between 2008 and 2010, with excluding mortal individuals within 2 years of CAD. It assessed all-cause mortality, CAD-specific mortality, all-cause hospitalization, and CAD-specific hospitalization over a two-year follow-up period.
Results: Hazard ratios (HRs) for all-cause mortality were lower in the "before CAD" (HR 0.93, 95% CI 0.89–0.97), "within one month" (HR 0.76, 95% CI 0.67–0.87), and "after one month" (HR 0.52, 95% CI 0.49–0.54) groups compared to the "no depression" group. Women had significantly lower HRs for all-cause and CAD-specific mortality. The "after one month" group showed a higher risk for all-cause hospitalization. Socioeconomic status, comorbidities, and age significantly influenced outcomes.
Conclusion: Depression in CAD patients who survived beyond two years appeared to confer a protective effect on mortality. These findings suggest that there may be other confounding factors that influence the prognosis of 2-year survival CAD patients. Further research may explore the mechanisms underlying these protective effects to improve clinical practices.

1. Introduction

Coronary artery disease (CAD) and depression frequently coexist, significantly impacting health outcomes and quality of life.[1] These conditions are significant contributors to the global disease burden.[2] Their interplay complicates disease management and worsens prognoses.[3]

CAD individuals with depression have at least twice a higher mortality risk compared with those without depression.[4,5] Individuals with CAD who experienced depression may have their CAD prognosis influenced by the timing of developing depression.[6,7] The timing of developing depression about CAD diagnosis — whether it occurs before, concurrently, or after the diagnosis of CAD — may have differential impacts on patients' survival rates.[7–9]

Previous studies have shown that 1- to 2-year mortality in CAD patients is affected by depression onset at different times.[7–9] However, no study has explored whether the mortality of CAD patients who survive beyond two years is still related to depression developing at different times. This study aims to fill this gap by examining the relationship between depression onset at different times and mortality in CAD patients who survive 2 years, with follow-up for an additional 2 years.

2. Materials and methods

2.1. Database and ethics approval

The research used data from Taiwan's National Health Insurance Research Database (NHIRD). Established in March 1995, the National Health Insurance[10] program is a single-payer system covering over 99% of Taiwan's 23 million residents. The NHIRD anonymizes individual identities and contains claims data based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Medical specialists and peer reviewers review insurance claims to ensure accuracy. The NHIRD's diagnoses have been validated by numerous studies,[11–13] making it a suitable tool for this research.

This research upheld strict ethical standards. Approved by the National Yang-Ming University-Joint Institutional Review Board (YM 105043E), it used de-identified NHI data to ensure patient privacy. A formal written waiver of consent has been granted, respecting pa-

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tient autonomy. Ethical considerations were meticulously followed to maintain the study's integrity.

2.2. Study design and participants

This nationwide population-based retrospective cohort study examined the relationship between 2-year CAD and subsequent mortality risk with depression developing at different times. Using NHIRD data from January 1, 2007, to December 31, 2014, it included individuals aged 20+ diagnosed with CAD between January 1, 2008, and December 31, 2010. The index date was the first CAD diagnosis, and only those with at least two CAD diagnoses within 30 days were included for validity. Individuals diagnosed in 2007 were excluded to ensure new onset. The study also excluded individuals who were mortalities within two years of the CAD diagnosis to assess the impact of depression developing at different time points on the subsequent 2-year prognosis.

In this study, we coded the diagnosis of CAD by ICD-9-CM code which includes acute myocardial infarction (AMI) (ICD-9-CM code 410. X), other acute and subacute forms of ischemic heart disease (ICD-9-CM code 411. X), old myocardial infarction (ICD-9-CM code 412. X), angina pectoris (ICD-9-CM code 413. X), or other forms of chronic ischemic heart disease (ICD-9-CM code 414. X). Meanwhile, a depressive disorder was defined as major depressive disorder, single episode (ICD-9-CM code 296.2x); major depressive disorder, recurrent episodes (ICD-9-CM code 296.3x); atypical depressive disorder (ICD-9-CM code 296.82); dysthymic disorder (ICD-9-CM code 300.4); adjustment disorder (ICD-9-CM code 309. x); and depressive disorder not classified elsewhere (ICD-9-CM code 311).

In this study, individuals with CAD were divided into four groups based on the timing of depression onset. The "before CAD" group was defined as depression before CAD onset between January 1, 2007, and December 31, 2010, with CAD diagnosed between January 1, 2008, and December 31, 2010, excluding mortal CAD individuals within two years after the onset of CAD. The "within one month" group was defined as depression developing within one month after CAD diagnosis between January 1, 2008, and January 31, 2011. The "after one month" group was defined as depression developing more than one month after CAD diagnosis between February 1, 2008, and December 31, 2012. The "no depression" group was defined as no depression between January 1, 2007, and December 31, 2014, with CAD diagnosed during the same period. The one-month timeframe aligns with the research conducted by Parker et al.[7] In their study, they found a strong correlation between the development of depression within a month after an acute coronary syndrome event and subsequent cardiovascular outcomes.

2.3. Outcome variables and other covariates

The four groups, "no depression," "before CAD," "within one month," and "after one month" were followed for two years from January 1, 2010, to December 31, 2014, to examine their relationships with all-cause mortality, CAD-specific mortality, all-cause hospitalization, and CAD-specific hospitalization.

We collected demographic factors such as age, sex, Charlson Comorbidity Index (CCI) score, and insurance payment bracket to assess their impact on mortality two years after CAD onset, with and without depression. Participants were categorized into age groups: 20–44, 45–64, 65–74, and ≥ 75 years. The CCI was used to evaluate comorbidities.[14–18] Insurance payment bracket, representing monthly income, were divided into four categories: low-income households, < 17,280 New Taiwan Dollars (NTD) (540.17 United States dollar, USD), 17,280 (540.17 USD)–33,299 NTD (1,040.95 USD), and ≥ 33,300 NTD (1,040.95 USD). This data helps investigate mortality covariates.

Table 1 presented data for 254,084 individuals in the "no depression" group, 14,554 in the "before CAD" group, 1,839 in the "within one month" group, and 17,427 in the "after one month" group, all followed by two years from the 2-year after CAD index date.

2.4. Statistical analysis

The analysis used the SAS statistical package (SAS Systems for Windows, version 9.2; Cary, NC, USA). We used the chi-square test to examine the demographic information of the four independent variable groups in the study. We used univariate Cox proportional hazards regression to calculate the hazard ratios (HRs) for further

Table 1
Sociodemographic data for CAD individuals with depression developing at different time points or without depression.

	No depression group	Before CAD group	Within one month group	After one month group	p
Gender					< 0.0001
Men (n = 159,533)	90.81%	3.85%	0.48%	4.86%	
Wimen (n = 128,371)	85.08%	6.55%	0.83%	7.54%	
Age					< 0.0001
20–44 (n = 27,006)	86.54%	5.37%	1.16%	6.93%	
45–64 (n = 125,445)	88.32%	4.93%	0.66%	6.09%	
65–74 (n = 66,574)	88.03%	5.06%	0.55%	6.36%	
≥ 75 (n = 72,570)	89.09%	5.07%	0.50%	5.34%	
Income (USD [a])					< 0.0001
Low-income household (n = 3,731)	80.17%	11.53%	0.88%	7.42%	
< 540.17 (n = 69,546)	86.94%	5.86%	0.66%	6.53%	
540.17–1040.95 (n = 137,699)	88.56%	4.79%	0.67%	5.98%	
> 1040.95 (n = 80,619)	89.34%	4.44%	0.56%	5.66%	
Comorbidity					< 0.0001
CCI = 0 (n = 116,702)	89.28%	4.03%	0.72%	5.97%	
CCI = 1 (n = 73,367)	87.98%	5.05%	0.67%	6.29%	
CCI = 2 (n = 41,943)	87.80%	5.65%	0.59%	5.96%	
CCI = 3 (n = 25,819)	87.18%	6.12%	0.44%	6.27%	
CCI = 4 (n = 33,764)	86.90%	6.91%	0.50%	5.69%	

[a] Exchange rate (the average exchange rate of 2008, 2009 and 2010) as 31.99 NT to 1 USD according to http://www.econ.sinica.edu.tw/content/economicdata/contents/2013090215155290268/?MSID=20130909141419617 53&R=4

mortality of individuals in the four independent variable groups. In the multivariate Cox proportional hazards regression model, we adjusted age, sex, income, and CCI as covariates. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Sociodemographic findings for individuals of CAD and with depression developed at various time points or without depression

The sociodemographic data for the "no depression," "before CAD," "within one month," and "after one month" groups is shown in Table 1. Women with CAD accounted for 85.08% in the "no depression" group, 6.55% in the "before CAD" group, 0.83% in the "within one month" group, and 7.54% in the "after one month" group. Corresponding percentages for men were 90.81%, 3.85%, 0.48%, and 4.86% in the respective groups. It seemed that men with CAD had a higher rate than women in the "no depression" group, but women had a higher likelihood of developing depression before or after CAD.

Individuals aged 20–44 had higher rates in the "before CAD," "within one month," and "after one month" groups. Those aged 75 and older had a higher rate with no depression but lower rates in the "within one month" and "after one month" groups, except in the "before CAD" group.

In terms of monthly income, individuals with monthly income over 1040.95 USD represented 89.34% of the "no depression" group, a higher percentage than other income subgroups. It seemed that individuals with a higher monthly income had lower rates compared to other income subgroups in the "before CAD," "within one month," and "after one month" groups. However, the low-income household subgroup had higher rates than other income subgroups in the same time frame.

Individuals without comorbidity (CCI = 0) had a rate of 89.28% in the "no depression" group, which was higher than the rates for those with comorbidities. In the "no depression" group, individuals with a high comorbidity (CCI = 4) had a lower rate of 86.90% compared to those with fewer other comorbidities.

3.2. The risk factors for all-cause mortality, CAD-specific mortality, all-cause hospitalization, and CAD-specific hospitalization

In this study, the "no depression" group had significantly higher HR of all-cause mortality than the other three groups. The HR of all-cause mortality in "before CAD" group, "within one month" group, and "after one month" group compared to that in "no depression" group was 0.93 (95% CI 0.89–0.97, $p = 0.0002$), 0.76 (95% CI 0.67–0.87, $p < .0001$) and 0.52 (95% CI 0.49–0.54, $p < .0001$), respectively, as shown in Table 2. Women had significantly lower HR (0.84, 95% CI 0.83–0.86, $p < 0.0001$) of all-cause mortality than men. The HR for all-cause mortality is positively correlated with aging and comorbidities; conversely, it decreases as monthly income rises.

Table 3 presents the results of both univariate and multivariate analyses of the risk factors for CAD-specific mortality among four independent groups. The "no depression" group had a significantly higher HR of CAD-specific mortality compared to the other three groups. Specifically, the HR of CAD-specific mortality in the "before CAD" group, "within one month" group, and "after one month" group, compared to that in the "no depression" group, was 0.80 (95% CI 0.72–0.89, $p < .0001$), 0.45 (95% CI 0.30–0.69, $p = 0.0003$), and 0.27 (95% CI 0.23–0.32, $p < .0001$), respectively. Furthermore, the study found that women had a significantly lower HR (0.79, 95% CI 0.76–0.83, $p < .0001$) of CAD-specific mortality compared to men. Addi-

Table 2
Univariate analysis and multivariate analysis of the risk factors for all-cause mortality among CAD individuals with depression developing at different time points or without depression.

Predictive variable	Univariate analysis		Multivariate analysis [b]	
	HR (95% CI)	p	HR (95% CI)	p
Depressive disorder				
No depression group (ref.)				
Before CAD group	1.03 (0.99–1.07)	0.1419	0.93 (0.89–0.97)	0.0002
Within one month group	0.69 (0.60–0.78)	< .0001	0.76 (0.67–0.87)	< .0001
After one month group	0.51 (0.48–0.53)	< .0001	0.52 (0.49–0.54)	< .0001
Sex				
Men (ref.)				
Women	0.89 (0.87–0.91)	< .0001	0.84 (0.83–0.86)	< .0001
Age				
20–44 (ref.)				
45–64	1.65 (1.54–1.76)	< .0001	1.38 (1.29–1.49)	< .0001
65–74	3.81 (3.56–4.07)	< .0001	2.57 (2.39–2.77)	< .0001
≥ 75	8.45 (7.91–9.02)	< .0001	5.22 (4.86–5.61)	< .0001
Income (USD [a])				
Low-income household (ref.)				
< 540.17	0.77 (0.73–0.82)	< .0001	0.72 (0.67–0.76)	< .0001
540.17–1040.95	0.63 (0.60–0.67)	< .0001	0.71 (0.67–0.75)	< .0001
> 1040.95	0.43 (0.40–0.46)	< .0001	0.62 (0.58–0.66)	< .0001
Comorbidities				
CCI = 0 (ref.)				
CCI = 1	2.37 (2.29–2.46)	< .0001	1.88 (1.82–1.95)	< .0001
CCI = 2	4.19 (4.06–4.34)	< .0001	2.94 (2.84–3.04)	< .0001
CCI = 3	5.51 (5.32–5.71)	< .0001	3.72 (3.59–3.86)	< .0001
CCI = 4	8.20 (7.94–8.47)	< .0001	5.63 (5.45–5.81)	< .0001

[a] Exchange rate (the average exchange rate of 2008, 2009 and 2010) as 31.99 NT to 1 USD according to http://www.econ.sinica.edu.tw/content/economicdata/contents/2013090215155290268/?MSID=2013090914141961753&R=4
[b] Multivariate analysis was adjusted for age, sex, monthly income, and comorbidities.

Table 3
Univariate analysis and multivariate analysis of the risk factors for CAD-specific mortality among CAD individuals with depression developing at different time points or without depression.

Predictive variable	Univariate analysis		Multivariate analysis [b]	
	HR (95% CI)	p	HR (95% CI)	p
Depressive disorder				
No depression group (ref.)				
Before CAD group	0.89 (0.80–0.99)	0.0341	0.80 (0.72–0.89)	< .0001
Within one month group	0.38 (0.24–0.58)	< .0001	0.45 (0.30–0.69)	0.0003
After one month group	0.26 (0.22–0.30)	< .0001	0.27 (0.23–0.32)	< .0001
Gender				
Men (ref.)				
Women	0.81 (0.78–0.85)	< .0001	0.79 (0.76–0.83)	< .0001
Age				
20–44 (ref.)				
45–64	1.76 (1.50–2.07)	< .0001	1.44 (1.21–1.72)	< .0001
65–74	3.85 (3.29–4.52)	< .0001	2.46 (2.06–2.93)	< .0001
≥ 75	8.84 (7.57–10.32)	< .0001	4.91 (4.13–5.85)	< .0001
Income (USD [a])				
Low-income household (ref.)				
< 540.17	0.85 (0.72–0.99)	0.0412	0.83 (0.70–0.97)	0.6679
540.17–1040.95	0.66 (0.57–0.78)	< .0001	0.81 (0.69–0.95)	0.7334
> 1040.95	0.48 (0.41–0.56)	< .0001	0.76 (0.65–0.90)	0.5833
Comorbidities				
CCI = 0 (ref.)				
CCI = 1	3.70 (3.38–4.05)	< .0001	2.96 (2.70–3.24)	< .0001
CCI = 2	6.75 (6.18–7.39)	< .0001	4.62 (4.22–5.06	< .0001
CCI = 3	8.35 (7.61–9.16)	< .0001	5.60 (5.09–6.15)	< .0001
CCI = 4	11.09 (10.17–12.09)	< .0001	7.27 (6.65–7.94)	< .0001

[a] Exchange rate (the average exchange rate of 2008, 2009 and 2010) as 31.99 NT to 1 USD according to http://www.econ.sinica.edu.tw/content/economicdata/contents/2013090215155290268/?MSID=2013090914141961753&R=4
[b] Multivariate analysis was adjusted for age, sex, monthly income, and comorbidities.

tionally, the HR of CAD-specific mortality was positively correlated with aging and comorbidities, and negatively correlated with monthly income, similar to the HR of all-cause mortality.

In Table 4, it was observed that the risk of all-cause hospitalization in the "after one month" group was significantly higher (HR 1.21, 95% CI 1.16–1.26, p < .0001) compared to the "no depression" group. The HR of all-cause hospitalization was not statistically different in the "before CAD" group and "within one month" group compared to the "no depression" group. Women had a significantly lower risk (HR 0.77, 95% CI 0.76–0.79, p < .0001) of all-cause hospitalization than men. The HR of all-cause hospitalization in individuals aged 45 and above was significantly higher than in those aged 20– 44. The HR for those aged 45–64, 65–74, and 75 and above was 1.11 (95% CI 1.06–1.15, p < .0001), 1.12 (95% CI 1.07–1.17, p < .0001), and 1.07 (95% CI 1.02–1.12, p = 0.0034), respectively. The HR of all-cause hospitalization did not show a significant difference as monthly income increased. The HR of all-cause hospitalization increased in a positively correlated manner with the number of comorbidities.

The HR of CAD-specific hospitalization among the four independent groups was not statistically different, as shown in Table 5. Women had significantly lower HR (0.63, 95% CI 0.61–0.64, p < .0001) of CAD-specific hospitalization than men. The HR of CAD-specific hospitalization increased positively correlated with aging and comorbidities. The HR of CAD-specific mortality was not statistically different compared to the four monthly income subgroups.

4. Discussion

4.1. Sociodemographic findings

The sociodemographic findings of this study reveal significant patterns in the relationship between CAD and depression developing at different time points, highlighting differences based on sex, age, income, and comorbidity status. Regarding sex disparity, men had a high prevalence in the "no depression" group, with 90.81% compared to 85.08% for women. However, women with CAD had a higher likelihood of developing depression either before or after the onset of CAD. Specifically, 6.55% of women were in the "before CAD" group compared to 3.85% of men, while 7.54% of women were in the "after one month" group compared to 4.86% of men. This suggests that depression is more prevalent among women with CAD than men. This aligns with existing literature suggesting women are more susceptible to depression, particularly following a significant health event like CAD.[19]

As to age distribution, younger individuals (aged 20–44) showed higher rates of depression in the "before CAD" group, "within one month" group, and "after one month" group compared to the other three age subgroups. Conversely, older individuals (≥ 75 years) had a higher prevalence in the "no depression" group. This age-related disparity indicates that younger CAD patients are more susceptible to developing depression. This finding suggests that younger individuals may be more prone to experiencing depression immediately following a CAD diagnosis, possibly due to the abrupt lifestyle changes and psychological impact associated with such a diagnosis at a relatively younger age.[20,21]

Individuals with higher monthly incomes (1,040.95 USD) had lower rates of depression compared to those with lower incomes. The low-income household subgroup had a higher incidence of depression across the "before CAD", "within one month", and "after one month" groups. This suggests a socioeconomic gradient where lower income is associated with higher depression rates among CAD patients, highlighting the compounded health challenges faced by these individuals who may not have enough financial support to receive medical services.[22]

Table 4
Univariate analysis and multivariate analysis of the risk factors for all-cause hospitalization among CAD individuals with depression developing at different time points or without depression.

Predictive variable	Univariate analysis		Multivariate analysis [b]	
	HR (95% CI)	p	HR (95% CI)	p
Depressive disorder				
No depression group (ref.)				
Before CAD group	0.97 (0.93–1.02)	0.2014	0.99 (0.94–1.03)	0.5920
Within one month group	0.83 (0.72–0.96)	0.0108	0.90 (0.78–1.04)	0.1422
After one month group	1.17 (1.13–1.22)	< .0001	1.21 (1.16–1.26)	< .0001
Sex				
Men (ref.)				
Women	0.79 (0.77–0.81)	< .0001	0.77 (0.76–0.79)	< .0001
Age				
20–44 (ref.)				
45–64	1.12 (1.07–1.16)	< .0001	1.11 (1.06–1.15)	< .0001
65–74	1.15 (1.10–1.20)	< .0001	1.12 (1.07–1.17)	< .0001
≥ 75	1.12 (1.07–1.17)	< .0001	1.07 (1.02–1.12)	0.0034
Income (USD [a])				
Low-income household (ref.)				
< 540.17	0.96 (0.89–1.04)	0.2873	1.00 (0.92–1.08)	0.9020
540.17–1040.95	0.93 (0.86–1.00)	0.0523	0.98 (0.91–1.06)	0.6799
> 1040.95	0.91 (0.84–0.98)	0.0184	0.97 (0.90–1.05)	0.4290
Comorbidities				
CCI = 0 (ref.)				
CCI = 1	1.30 (1.27–1.34)	< .0001	1.28 (1.24–1.32)	< .0001
CCI = 2	1.42 (1.38–1.47)	< .0001	1.41 (1.36–1.45)	< .0001
CCI = 3	1.44 (1.39–1.49)	< .0001	1.43 (1.38–1.49)	< .0001
CCI = 4	1.56 (1.51–1.61)	< .0001	1.56 (1.51–1.62)	< .0001

[a] Exchange rate (the average exchange rate of 2008, 2009 and 2010) as 31.99 NT to 1 USD according to http://www.econ.sinica.edu.tw/content/economicdata/contents/2013090215155290268/?MSID=2013090914141961753&R=4
[b] Multivariate analysis was adjusted for age, sex, monthly income, and comorbidities.

Table 5
Univariate analysis and multivariate analysis of the risk factors for CAD-specific hospitalization among CAD individuals with depression developing at different time points or without depression.

Predictive variable	Univariate analysis		Multivariate analysis [b]	
	HR (95% CI)	p	HR (95% CI)	p
Depressive disorder				
No depression group (ref.)				
Before CAD group	0.97 (0.93–1.02)	0.2430	0.97 (0.92–1.02)	0.2058
Within one month group	0.85 (0.74–0.98)	0.0200	0.89 (0.77–1.02)	0.0908
After one month group	0.95 (0.91–0.99)	0.0206	0.99 (0.94–1.03)	0.4829
Gender				
Men (ref.)				
Women	0.64 (0.63–0.66)	< .0001	0.63 (0.61–0.64)	< .0001
Age				
20–44 (ref.)				
45–64	1.31 (1.26–1.37)	< .0001	1.30 (1.24–1.36)	< .0001
65–74	1.47 (1.40–1.54)	< .0001	1.39 (1.32–1.46)	< .0001
≥ 75	1.72 (1.64–1.80)	< .0001	1.52 (1.45–1.60)	< .0001
Income (USD [a])				
Low-income household (ref.)				
< 540.17	0.91 (0.83–1.00)	0.0524	0.98 (0.89–1.08)	0.6679
540.17–1040.95	0.85 (0.77–0.93)	0.0004	0.98 (0.90–1.08)	0.7334
> 1040.95	0.82 (0.74–0.90)	< .0001	0.97 (0.89–1.07)	0.5833
Comorbidities				
CCI = 0 (ref.)				
CCI = 1	1.27 (1.23–1.30)	< .0001	1.23 (1.20–1.26)	< .0001
CCI = 2	1.61 (1.56–1.67)	< .0001	1.53 (1.48–1.59)	< .0001
CCI = 3	1.76 (1.69–1.83)	< .0001	1.68 (1.62–1.74)	< .0001
CCI = 4	2.29 (2.22–2.37)	< .0001	2.18 (2.10–2.26)	< .0001

[a] Exchange rate (the average exchange rate of 2008, 2009 and 2010) as 31.99 NT to 1 USD according to http://www.econ.sinica.edu.tw/content/economicdata/contents/2013090215155290268/?MSID=2013090914141961753&R=4
[b] Multivariate analysis was adjusted for age, sex, monthly income, and comorbidities.

The "no depression" group had a higher proportion of individuals without comorbidities (CCI = 0), at 89.28%. Higher comorbidity scores were more common among those with depression, indicating that individuals with multiple health issues are more likely to ex-

perience depression alongside CAD.

4.2. Risk factors for mortality and hospitalization

The hazard ratios (HR) for all-cause mortality indicate that CAD patients without depression have significantly higher mortality rates compared to those with depression at various time points relative to their CAD diagnosis. Specifically, the HR for all-cause mortality was highest for the "no depression" group and progressively lower for those with the "before CAD" group, "within one month" group, and "after one month" group. This suggests that depression, despite its negative connotations, might confer a protective effect on mortality in CAD patients who were still surviving after 2 years of onset, potentially due to increased medical attention and management of both conditions in this study. These findings were not inconsistent with previous findings.[5,7] Several reasons might explain these differences. First, those who survive the initial two years after CAD onset may represent a resilient subgroup with better overall health or more effective coping mechanisms, including those who manage their depression well. This survivor bias might contribute to the observed lower mortality rates in the later period, which is also found in the nephrology literature.[23] Second, for individuals with CAD who survive longer than two years, comorbid depression might serve as a protective factor. This counterintuitive finding could be due to increasing social support that comes with a diagnosis of depression, potentially improving their overall prognosis. Individuals with depression might receive more comprehensive care, including mental health support,[24] which could enhance their survival rates beyond the acute phase. Third, depression may affect individuals with CAD strongly within the first two years after CAD onset. However, from de Jager et al.'s study, the association of depression mortality would weaken after adjusting for anxiety.[9,25] There may be more confounding factors we need to further explore. Fourth, no matter whether it was underdiagnosed or cultural effects, Taiwan has a lower depression rate, not only in the general population but also among CAD patients, compared to Western countries,[26] which could influence the observed relationships between CAD, depression, and mortality. Fifth, although antidepressants didn't significantly influence CAD outcomes in the CAD population with depression,[27] it could be a confounding factor that needs to be further addressed.

Women consistently had lower HRs for all-cause mortality, CAD-specific mortality, and CAD-specific hospitalization compared to men, indicating better survival outcomes for female individuals with CAD. This finding aligns with previous research showing gender differences in cardiovascular outcomes, possibly due to biological, behavioral, and treatment-related factors, similar to the previous studies,[28–30] although there was a methodology difference.

Age and comorbidities were positively correlated with increased HRs for all-cause mortality and CAD-specific mortality, reaffirming the detrimental impact of aging and multiple health conditions on patient outcomes. Interestingly, higher monthly income was associated with lower HRs for all-cause and CAD-specific mortality, underscoring the influence of socioeconomic factors on health outcomes.

Regarding CAD-specific hospitalization, the HRs were similar across the four groups, suggesting that the timing of depression onset does not significantly affect the likelihood of subsequent hospitalizations for individuals with CAD after 2-year survival. However, the "after one-month" group had a significantly higher HR for all-cause hospitalization, indicating a delayed but substantial impact of depression on overall health and healthcare utilization.

4.3. Strengths and limitations of this study

The strengths of the study are as follows. First, this study utilized data from the NHIRD of Taiwan, which covers over 99% of the population. This large, nationwide cohort ensures robust statistical power and generalizability of the findings. Second, by categorizing individuals based on the timing of depression onset relative to their CAD diagnosis, this study provides a detailed examination of how the temporal relationship between these conditions affects long-term mortality. Third, unlike previous studies that focused on short-term outcomes, this study followed 2-year survival participants for the next two years, offering insights into the long-term impacts of depression on CAD prognosis. Fourth, the analysis accounted for various demographic and clinical factors, including age, sex, income, and comorbidities, enhancing the reliability of the findings.

There were also some limitations. First, as a retrospective cohort study, the findings may be subject to biases inherent in observational research, such as selection bias and residual confounding. Second, the NHIRD lacks detailed information on psychosocial factors, which could influence both depression and CAD outcomes. This limitation prevents a more comprehensive understanding of psychological and physical health interplay. Third, while the study's large sample size and nationwide coverage enhance its generalizability within Taiwan, the findings may not fully apply to populations with different healthcare systems and socio-cultural contexts.

4.4. Implications for clinical practice and future research

This nationwide population-based retrospective cohort study revealed that the mortality risk of individuals with CAD for 2-year survival who suffered depression at different time points of CAD was significantly lower than that of those without depression. From previous studies, individuals with CAD comorbid with depression had significantly higher mortality for 2-year follow-up. However, these findings showed that comorbid depression may be a protective factor for further mortality in CAD individuals who were immortal after 2 years. For clinical practice, this indicates the need for a nuanced approach to managing depression in CAD patients, considering potential long-term benefits. Future research should explore the underlying mechanisms and verify these protective effects to better inform treatment strategies.

In conclusion, this study emphasizes the higher mortality rate of individuals with CAD for 2-year survival without suffering from depression compared to those with depression at different times. Men, older age, low-income households, and high comorbidity are associated with higher mortality rates. A holistic approach to patient care, integrating mental health support with cardiovascular treatment, is essential for improving overall patient outcomes.

Declaration of any potential financial and non-financial conflicts of interest

None.

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