Non-cardiac comorbid health outcomes and prevalence after myocardial infarction: an umbrella review

H. JEON[1], H. LEE[2,3], H. YANG[2,3], M. RAHMATI[4,5], M.S. KIM[6,7], Y. CHOI[2,8], J.M. CHO[1], D.K. YON[2,3,9]

[1]Department of Internal Medicine, Division of Cardiology, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, South Korea
[2]Center for Digital Health, Medical Science Research Institute, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea
[3]Department of Regulatory Science, Kyung Hee University, Seoul, South Korea
[4]Department of Physical Education and Sport Sciences, Faculty of Literature and Human Sciences, Lorestan University, Khoramabad, Iran
[5]Department of Physical Education and Sport Sciences, Faculty of Literature and Humanities, Vali-e-Asr University of Rafsanjan, Rafsanjan, Iran
[6]Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, MA, USA
[7]Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA
[8]Department of Korean Medicine, Kyung Hee University College of Korean Medicine, Seoul, South Korea
[9]Department of Pediatrics, Kyung Hee University College of Medicine, Seoul, South Korea

Hongki Jeon, Hyeri Lee, and Hwi Yang contributed equally as the first authors

Abstract. – OBJECTIVE: There exists limited comprehensive evidence on the potential association between non-cardiac comorbidities and myocardial infarction (MI). Thus, we conducted an umbrella review of existing meta-analyses to provide a broad understanding of non-cardiac health outcomes associated with MI.

MATERIALS AND METHODS: The primary focus on the prevalence of related health outcomes in patients with MI was systemically searched. Each original meta-analysis that was included had its methodological quality evaluated by a Measurement Tool Assessment Systematic Reviews 2 (AMSTAR2). To evaluate the certainty in the evidence for each outcome, we employed GRADE and the Joanna Briggs Institute Prevalence Critical Appraisal Tool. The protocol was registered in PROSPERO (CRD42023458642).

RESULTS: We identified seven meta-analyses comprising 126 studies with 336,581 participants from 22 countries and five continents. The pooled prevalence of comorbidities in patients with MI was 39% anxiety [95% confidence interval (CI), 30-48; GRADE, very low certainty], 29% depression (95% CI, 23-36; very low certainty), 39% frailty (95% CI, 24-55; very low certainty), and 23% failure of returning to work (95% CI, 16-29; very low certainty). The diagnosis of MI was associated with an increased risk of cognitive impairment (odds ratio, 1.45; 95% CI, 1.10-1.92; moderate certainty). Among frail patients, MI was associated with an increased risk of major bleeding (relative risk, 1.93; 95% CI, 1.08-3.45; low certainty) and mortality (relative risk, 2.29; 95% CI, 1.48-3.53; moderate certainty). However, we did not find any evidence of cancer risk associated with the development of MI.

CONCLUSIONS: Our umbrella meta-analysis provided comprehensive evidence of the association between MI and several non-cardiac health conditions. The robustness of our study is attributed to the integration of evidence across several studies, thus, these insights offer valuable treatment options for policymakers and physicians to develop personalized health strategies.

Key Words:
Myocardial infarction, Umbrella review, Meta-analysis.

Introduction

Myocardial infarction (MI) is one of the life-threatening cardiovascular events and the most severe clinical presentation of coronary artery disease (CAD)[1]. Because of its potentially life-threatening consequences, previous research has primarily centered on examining risk factors

Corresponding Authors: Jin-Man Cho, MD; e-mail: cardiocho@khu.ac.kr;
Dong Keon Yon, MD, Ph.D; e-mail: yonkkang@gmail.com

and investigating critical prognostic outcomes, including mortality, stroke, and the recurrence of MI[2]. Advancements in treatment strategies have tremendously reduced MI-associated mortality and cardiovascular adverse outcomes[3]. Consequently, patients undergoing treatment for MI have an extended life expectancy[3], reflecting improvement in the overall survival rate and well-being and quality of life of patients.

In addition to cardiovascular complications, several studies have investigated the wider systemic comorbidities of MI, including depression and cancer[4,5]. An umbrella review offers the potential to enhance our understanding of uncertainties, biases, and areas of limited knowledge[6]. As such, we conducted an umbrella review of existing meta-analyses to provide a comprehensive understanding of non-cardiac comorbidities linked to MI. Furthermore, we provided evidence that can serve as the basis for developing a holistic treatment strategy for MI survivors.

Materials and Methods

Literature Search and Selection Criteria

This umbrella review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines from 2020[7]. The protocol was registered in the PROSPERO database with registration number CRD42023458642. Two independent researchers, H.J. and H.L., systematically searched PubMed/MEDLINE, Embase, CINAHL, and Google Scholar databases through July 2023 for meta-analyses of the cohort, case-control, and cross-sectional studies examining the various non-cardiac comorbid health outcomes after MI diagnosis. The search strategy was as follows: "meta-analysis" AND ("myocardial infarction" OR "MI" OR "STEMI" OR "NSTEMI" OR "ischemic heart disease" OR "myocardial ischemia" OR "acute coronary syndrome" OR "coronary") and their variations. Two researchers manually examined the references of eligible articles and rigorously reviewed the titles, abstracts, and full texts.

The inclusion criteria were studies detailing any of the following metrics: proportion, prevalence, odds ratio (OR), and relative risk ratio (RR) or hazard ratio (HR). Several non-cardiac comorbidities under consideration ranged from neurological (e.g., dementia and Parkinson's disease), psychiatric (e.g., depression, bipolar disorders, anxiety disorder, and schizophrenia), neurological (e.g., dementia and Parkinson's disease), allergic (e.g., food allergy and asthma), infections (e.g., candidiasis), cancer (e.g., overall cancer and breast cancer), gastrointestinal (e.g., irritable bowel syndrome), sleep (e.g., total sleep time, time in bed, and sleep efficiency), and including the quality of life outcomes such as return to work[8].

Quality Assessment

Researchers H.J. and H.L. independently assessed the methodological soundness of each meta-analysis using the "A Measurement Tool Assessment Systematic Reviews 2 (AMSTAR2)" checklist and "Joanna Briggs Institute Prevalence Critical Appraisal Tool"[9,14]. Discrepancies in evaluations were resolved and the consensus was reached with the help of a third researcher, D.K.Y. In addition, we applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to gauge the evidence quality for every outcome[8]. The modified GRADE method was used to categorize evidence certainty as high, moderate, low, or very low. Methodologically rigorous large-scale randomized controlled trials received a high-grade designation, whereas smaller intervention trials were considered moderate. Heterogeneity > 75% for continuous outcomes and 50% for binary outcomes were flagged as inconsistency. Indirectness was attributed to noticeable differences between study groups. The imprecision criteria were met when the participant count was less than 1,000. Funnel plots, Egger's test *p*-values, and *p*-curve analyses were used to detect the publication bias. We established a dose-response relationship for the effect size, indicating a gradual escalation in outcome gravity. Moreover, the presence of probable residual confounding factors further confirmed the reliability of evidence's reliability[15-17].

Patient and Public Involvement

Patients were not involved while forming the research question, determining outcome measures, or designing and executing the study. Patients were not consulted during the interpretation of the results or the writing phase. However, study findings will be accessible to participants and relevant communities when requested.

Data Extraction

For each identified study, we collected information including the publication year, number of primary studies included, observed outcomes, country of origin, the count of cases and participants, study methodology, the employed effect estimation model (random or fixed effects), degree of heterogeneity, and the most adjusted effect size accompanied by a 95% confidence interval (CI). The DerSimonian and Laird models for both random and fixed effects, as well as the Hartung-Knapp-Sidik-Jonkman model for random effects, were applied to minimize the risk of type I errors[7]. We refrained from re-analyzing the network or dose-dependent meta-analyses due to insufficient estimates and evidence.

Statistical Analysis

We made the following assessments to corroborate the primary findings: (1) Large heterogeneity was indicated if I^2 values exceeded 50, (2) the *p*-curve analysis was conducted to detect potential *p*-hacking[6], (3) 95% prediction interval (PI) was used to assess the uncertainty of the observed estimates and suggest directions for future research using Bayesian statistics, (4) publication bias was inferred if the Egger's *p*-value fell under 0.1[8]. We conducted evidence mapping following the modern standards to provide a comprehensive overview of the strength of evidence and the direction of associations[9]. All statistical evaluations were undertaken using the R software (version 4.2.2; R Foundation, Vienna, Austria); a two-sided *p*-value lower than 0.05 was considered significant[10-13].

Results

The initial database and manual search yielded 5,350 articles (Figure 1). After titles, abstracts, and full-text screenings, and removing duplicates, seven meta-analyses[18-24] of observational studies encompassing 126 original articles and 336,581 participants across 22 countries (Australia, Canada, China, Croatia, Denmark, France, Germany, Iran, Ireland, Israel, Italy, Japan, the Netherlands, New Zealand, Norway, Pakistan, Poland, South Korea, Spain, Sweden, the United Kingdom, and the United States and five continents (Africa, Asia, Europe, North America and

Table I. Description of total meta-analysis to investigate the potential association between patients with myocardial infarction and all-related prevalence.

Character outcome(prevalence)	First author	Published year	Included countries	AMSTAR2
Prevalence				
Anxiety	Lian et al[20]	2021	Australia, Canada, China, Denmark, Germany, Iran, Japan, Netherlands, Norway, Pakistan, South Korea, Sweden, United Kingdom, United States	High
Cancer	Li et al[18]	2019	Denmark, Norway, United States	High
Frailty	Yu et al[22]	2023	Australia, Japan, Netherlands, Poland, United States, Vietnam	Low
Depression	Feng et al[21]	2019	Australia, Canada, Denmark, Iran, Israel, Japan, Norway, Sweden, United Kingdom, United States	High
Return to work	Kai et al[23]	2022	Australia, China, Croatia, Denmark, France, Ireland, Iran, Italy, Japan, Netherlands, New Zealand, Poland, Spain, Sweden, United Kingdom, United States	Moderate
Risk				
Cognitive impairment or dementia	Deckers et al[24]	2017	Australia, Finland, Netherlands, United States	High
Cancer	Li et al[18]	2019	Denmark, Norway	High
Cancer (male)	Li et al[18]	2019	Denmark, Norway, Sweden	High
Cancer (female)	Li et al[18]	2019	Denmark, Norway, Sweden	High
Lung cancer (male)	Li et al[18]	2019	Denmark, Sweden	High
Lung cancer (female)	Li et al[18]	2019	Denmark, Sweden	High
Major bleeding (frail participants)	Yu et al[22]	2023	Japan	Low
Mortality (frail participants)	Yu et al[22]	2023	Japan, Netherlands, Vietnam	Low
Prostate cancer (male)	Li et al[18]	2019	Denmark, Sweden	High
Breast cancer (female)	Li et al[18]	2019	Denmark, Sweden	High

AMSTAR2, A Measurement Tool Assessment Systematic Reviews 2.

Oceania) were included. Table I and **Supplementary Table I** summarized the studies included in this umbrella review, offering key information such as outcomes, primary authors, publication years, countries involved, and Measurement Tool Assessment Systematic Reviews 2 (AMSTAR2) ratings.

Anxiety and Depression (Prevalence)

The study revealed a pooled prevalence of 39% [95% confidence interval (CI), 30-48] for anxiety and 29% (95% CI, 23-36) for depression among patients diagnosed with MI (Table II).

Frailty (Prevalence)

The pooled prevalence of frailty among older patients with MI after percutaneous coronary intervention was 39% (95% CI, 24-55), especially 46% (95% CI, 17-74) in patients with STEMI (Table II and **Supplementary Table II**).

Return to Work (Prevalence)

The pooled prevalence of return to work among patients with MI was 77% (95% CI, 71-84; Table II).

Cognitive Impairment and Dementia (Risk)

We found a 45% increased risk of developing cognitive impairment or dementia after MI [OR (95% CI, 1.10-1.92), Table II].

Cancer (Risk)

Our results demonstrated that the estimated overall cancer incidence rate after MI was 9% (95% CI, 7-11) and the relationship between MI and cancer incidence was uncertain (Table II). This is because several cancer types (for example, lung cancer) and MI share risk factors such as smoking history and are correlated. However, unlike previous literature, subgroup analysis by sex and cancer type conducted in

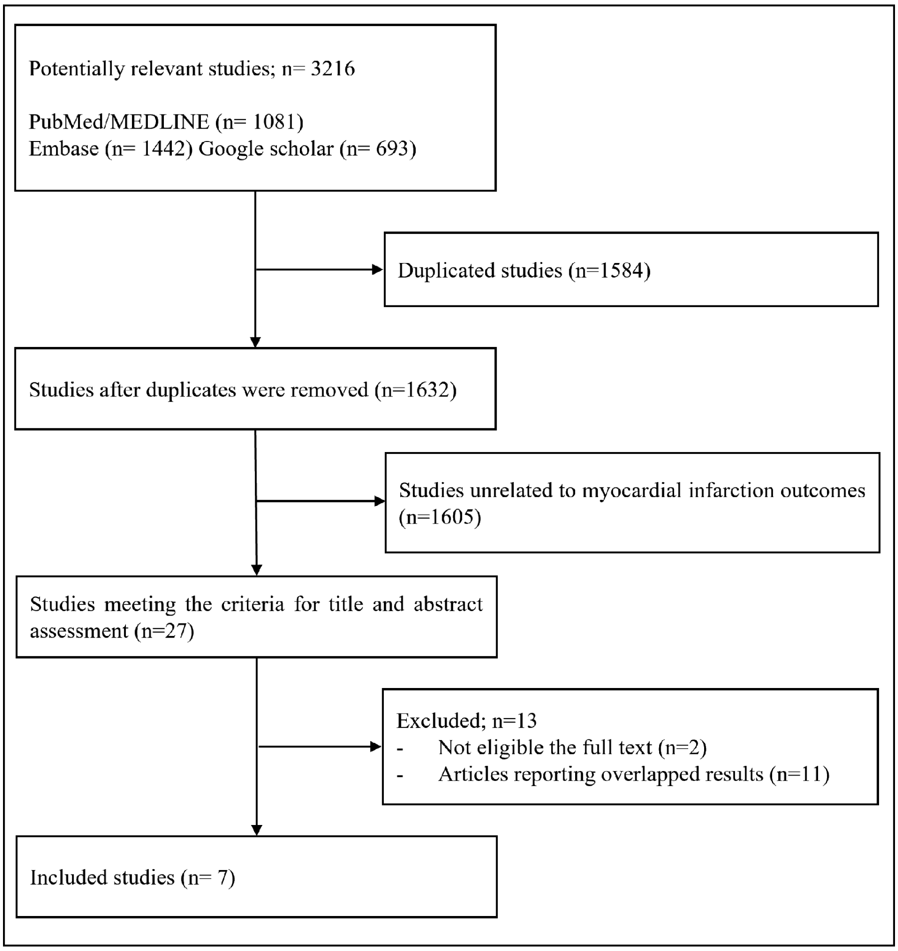

Figure 1. Study selection.

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Table II. Reanalysis of estimated effect using Der Simonian and Laird (DL) method and Hartung-Knapp-Sidik-Jonkman (HS) method, heterogeneity I^2, Egger's *p*-value, and 95% prediction interval.

Outcome	Included studies	Metrics	Total sample	Reported summary estimated effect (95% CI); random effect model	Re-analyzed summary estimated effect (95% CI) DL method			Re-analyzed summary estimated effect (95% CI) HS method; random-effect model	Heterogeneity I^2 (%)	Tau square, τ^2(%)	Egger's *p*-value	95% prediction interval	GRADE
					Fixed-effect model	Random-effect model	Largest study						
Prevalence													
Anxiety	18	Proportion	8,532	**0.38 (0.29 to 0.48)**	**0.36 (0.35 to 0.37)**	**0.39 (0.29 to 0.49)**	**0.11 (0.09 to 0.14)**	**0.39 (0.30 to 0.48)**	99.05	4.45	0.26	(0.25, 0.54)	Very low
Depression	19	Proportion	12,315	**0.29 (0.22 to 0.35)**	**0.28 (0.27 to 0.28)**	**0.29 (0.23 to 0.36)**	**0.22 (0.21 to 0.24)**	**0.29 (0.23 to 0.36)**	98.60	2.15	0.43	(0.21, 0.40)	Very low
Return to work	26	Proportion	26,001	**0.80 (0.74 to 0.86)**	**0.78 (0.78 to 0.79)**	**0.77 (0.71 to 0.84)**	**0.00 (0.00 to 0.00)**	**0.77 (0.71 to 0.84)**	99.25	2.67	0.68	(0.66, 0.86)	Very low
Frailty	9	Proportion	267,419	**0.39 (0.18 to 0.60)**	**0.23 (0.23 to 0.23)**	**0.39 (0.13 to 0.66)**	**0.10 (0.10 to 0.10)**	**0.39 (0.24 to 0.55)**	99.99	20.21	0.49	(0.11, 0.78)	Very low
Cancer	4	Proportion	221,994	**0.10 (0.08 to 0.11)**	**0.10 (0.10 to 0.10)**	**0.09 (0.08 to 0.11)**	**0.09 (0.09 to 0.09)**	**0.09 (0.07 to 0.11)**	93.12	0.02	0.67	(0.07, 0.13)	Very low
Risk													
Cognitive impairment or dementia	7	OR	20,225	**1.46 (1.16 to 1.84)**	**1.42 (1.21 to 1.68)**	**1.45 (1.16 to 1.82)**	**1.30 (1.00 to 1.90)**	**1.45 (1.10 to 1.92)**	36.12	0.03	0.52	(0.85, 2.49)	Moderate
Cancer (overall)	3	OR	220,913	1.08 (0.97 to 1.19)	**1.04 (1.02 to 1.06)**	1.08 (0.97 to 1.20)	0.97 (0.92 to 1.01)	1.08 (0.69 to 1.68)	90.04	0.66	0.81	(0.31, 3.73)	Low
Cancer (male)	4	OR	183,384	1.04 (0.99 to 1.10)	**1.04 (1.02 to 1.05)**	1.04 (0.99 to 1.09)	**1.03 (1.01 to 1.06)**	1.04 (0.93 to 1.16)	76.87	0.16	0.69	(0.85, 1.28)	Very low
Cancer (female)	4	OR	101,450	**1.10 (1.01 to 1.20)**	**1.09 (1.06 to 1.12)**	**1.10 (1.01 to 1.20)**	**1.08 (1.04 to 1.12)**	1.10 (0.89 to 1.36)	82.88	0.50	0.61	(0.77, 1.57)	Very low
Lung cancer (male)	3	OR	182,301	**1.12 (1.05 to 1.19)**	**1.14 (1.07 to 1.20)**	**1.13 (1.06 to 1.21)**	**1.19 (1.09 to 1.29)**	1.13 (0.97 to 1.32)	23.10	0.09	0.49	(0.63, 2.04)	Low
Lung cancer (female)	3	OR	100,786	**1.51 (1.15 to 1.99)**	**1.62 (1.54 to 1.71)**	**1.51 (1.15 to 1.99)**	**1.70 (1.60 to 1.90)**	1.51 (0.79 to 2.87)	92.49	5.31	0.66	(0.05, 16.30)	Very low
Prostate cancer (male)	3	OR	182,301	0.96 (0.85 to 1.09)	1.00 (0.99 to 1.01)	0.98 (0.91 to 1.05)	**1.00 (1.00 to 1.10)**	0.98 (0.76 to 1.25)	84.61	0.36	0.78	(0.39, 2.43)	Low
Breast cancer (female)	3	OR	100,786	0.94 (0.86 to 1.04)	0.95 (0.88 to 1.02)	0.94 (0.86 to 1.04)	1.00 (0.90 to 1.10)	0.94 (0.76 to 1.17)	38.47	0.27	0.03	(0.38, 2.33)	Low
Major bleeding (frail participants)	2	RR	3,186	**1.93 (1.29 to 2.90)**	**1.93 (1.29 to 2.90)**	**1.93 (1.29 to 2.90)**	**1.90 (1.22 to 2.90)**	**1.93 (1.08 to 3.45)**	< 0.001	-	-	-	Low
Mortality (frail participants)	6	RR	4,087	**2.29 (1.65 to 3.16)**	**2.17 (1.66 to 2.84)**	**2.29 (1.65 to 3.16)**	**1.81 (1.23 to 2.65)**	**2.29 (1.48 to 3.53)**	19.66	3.29	0.02	(1.15, 4.52)	Moderate

CI, confidence interval; DL, Der Simonian and Laird; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HS, Hartung-Knapp-Sidik-Jonkman; OR, odds ratio; RR, relative risk. The numbers in bold indicate a significant difference ($p < 0.05$).

Table III. Evidence maps of umbrella review by association between patients with myocardial infarction and all-related prevalence.

	OR (95% CI)	Proportion (95% CI)	Direction	Certainty of evidence
1. Prevalence				
Anxiety		**0.39 (0.30 to 0.48)**	-	Very low
Depression		**0.29 (0.23 to 0.36)**	-	Very low
Return to work		**0.77 (0.71 to 0.84)**	-	Very low
Frailty		**0.39 (0.24 to 0.55)**	-	Very low
Cancer		**0.09 (0.07 to 0.11)**	-	Very low
2. Risk				
Cognitive impairment or dementia	**1.45 (1.10 to 1.92)**		Association	Moderate
Cancer (overall)	1.08 (0.69 to 1.68)		Association	Low
Cancer (male)	1.04 (0.93 to 1.16)		No association	Very low
Cancer (female)	1.10 (0.89 to 1.36)		No association	Very low
Lung cancer (male)	1.13 (0.97 to 1.32)		No association	Low
Lung cancer (female)	1.51 (0.79 to 2.87)		No association	Very low
Prostate cancer (male)	0.98 (0.76 to 1.25)		No association	Low
Breast cancer (female)	0.94 (0.76 to 1.17)		No association	Low
Major bleeding (frail participants)	**1.93 (1.08 to 3.45)**		Association	Low
Mortality (frail participants)	**2.29 (1.48 to 3.53)**		Association	Moderate

CI, confidence interval; OR, odds ratio. The numbers in bold indicate a significant difference ($p < 0.05$). Color represented the levels of OR and proportion in data with statistical significance ($p < 0.05$).

this study did not confirm a statistically significant association with MI. Previous studies[18] have demonstrated that the incidence of cancer was highest in the first follow-up period (< 6 months). The possibility of overinterpretation due to surveillance bias in the included studies was considered.

Major Bleeding and Mortality Among Frail Older Population (Risk)

Frail older patients with MI who underwent coronary intervention had a 1.93-fold increase (95% CI, 1.08-3.45) risk of major bleeding and a 2.29-fold increase (95% CI, 1.48-3.53) of mortality.

AMSTAR2, GRADE Classification, Heterogeneity, Publication Bias, and Population-Attributable Fractions of Included Studies

AMSTAR2 had no "very high" or "very low" ratings, and the most common error was that the researchers did not list the ruled-out studies or justify their exclusion. In addition, funding information was missing in certain cases (**Supplementary Tables III**, **IV**, and **V**). **Supplementary Table VI** displays a breakdown of GRADE scores for each study (high confidence, 25%; moderate confidence, 60%; low confidence, 10%; very low confidence, 4.8%). We summarized several outcomes according to the confidence of evidence in Table III.

With the exception of three outcomes [all-cause mortality of frail participants, risk of adverse outcomes in frail participants, and risk of heart disease (angina and MI) and cognitive impairment or dementia], the shape of the p-curve was highly right-skewed for continuous ($p < 0.05$) and binomial tests ($p < 0.025$), indicating no evidence of p-hacking.

A re-analysis of the 24 outcomes using random effects analyses, demonstrated that 70.8% of the seven meta-analyses exhibited significant heterogeneity ($I^2 > 75$ for continuous, and $I^2 > 50$ for binary metrics). Egger's regression test revealed statistical evidence of publication bias in 23.8% of studies. The forest plot, funnel plot, and p-curve for each outcome are presented in the **Supplementary File.**

Discussion

To the best of our knowledge, this is the first comprehensive study to examine several non-cardiac comorbidities occurring after MI by conducting an umbrella review of seven meta-analyses with 126 studies across 22 countries. We conducted an umbrella meta-analysis to estimate the pooled prevalence of anxiety, depression, frailty, returning to work, and cancer. Anxiety (39%), depression (29%), frailty (39%), and failure to return to work (23%) were frequently observed following MI.

Next, we calculated the estimates for cognitive impairment, dementia, and cancer among patients with MI and for major bleeding and mortality among frail patients with MI. A notable 45% increase in the risk of cognitive impairment and dementia among patients with MI and an 80-90% increase in major bleeding and mortality among frail patients with MI were observed. The overall incidence rate of cancer following myocardial infarction was 9%, although statistically significant associations were not observed.

Plausible Underlying Mechanisms

Our comprehensive study indicated a potential association between MI and several non-cardiac comorbidities. This can be attributed to two main factors: distinguishable from the physiological effects of ischemic heart disease itself and the effects of medications taken post-myocardial infarction[25,26].

MI triggers an intricate cascade involving the autonomic nervous system, thereby promoting the activation of the sympathetic nervous system and concurrent withdrawal of the parasympathetic branch[27]. This resultant autonomic imbalance is marked by heightened sympathetic activity coupled with a diminished vagal tone, resulting in anxiety or depression[28,29]. Furthermore, an autonomic nervous system imbalance can be linked to reduced physical activity and cognitive function decline in older adults, thereby contributing to the development of frailty and dementia[30,31].

Most patients who experience MI are typically prescribed beta-blockers. Although beta-blockers do not impact depression or anxiety[32], these, especially early-generation beta-blockers, can lead to feelings of fatigue[32,33]. This either significantly delays the return to work or leads to failure.

Moreover, patients are often prescribed long-term antiplatelet agents, increasing the risk of bleeding[34]. Bleeding from antiplatelet therapy can worsen frailty. Conversely, frailty can exacerbate the risk of bleeding[35]. Bleeding events, including intracranial hemorrhage, can potentially contribute to cognitive impairment or dementia.

Implications for Clinicians and Policy Makers

Our findings highlight the requirement for a comprehensive management strategy to improve the quality of life of patients with MI[36]. This necessitates institutional support to facilitate patient engagement in cardiac rehabilitation initiatives. Cardiac rehabilitation programs should address not only cardiac recovery but also the rehabilitation of mood disorders, frailty, cognitive function, and the resumption of work[37]. Although there is no definitive consensus on the effectiveness of psychological counseling or physical exercise programs in enhancing the return-to-work process, a more sophisticated and personalized strategy should be devised based on the prevalence rates elucidated in this study.

Our findings did not establish a direct association between cancer and MI. Although MI itself may not directly influence cancer development, patients with MI often require long-term aspirin use[38]. The Aspirin in Reducing Events in the Elderly trial's findings on the effects of prolonged aspirin consumption demonstrated that, long-term aspirin use is associated with a substantial increase in cancer-related mortality[39]. Thus, screening for early cancer detection in patients who have received treatment for MI and have been visiting clinics for an extended period should not be overlooked[40].

Limitations and Strengths

Although our study offers valuable insights into the associations between MI and several factors, certain limitations should be acknowledged. First, most included studies were observational, which inherently introduced the potential for selection bias and confounding variables. Second, the heterogeneity in study designs, patient populations, and assessment methods across the reviewed literature could have affected the generalizability of our findings. Third, the possibility of publication bias cannot be completely ruled out because studies with significant results are more likely to be published, potentially leading to an overestimation of observed associations.

Despite these limitations, our study had several strengths that enhance the credibility of our findings. The umbrella review methodology allowed

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a comprehensive evaluation of a wide range of associations, synthesizing evidence from numerous studies. The incorporation of several factors, including depression, anxiety, frailty, cognitive impairment, return to work, and cancer, provides a comprehensive overview of the multifaceted impact of MI.

Conclusions

We investigated a wide range of non-cardiac comorbidities followed by MI using an umbrella review. The robustness of our study is attributed to the integration of evidence across several studies. This highlights the intricate interplay between MI and diverse comorbidities, such as anxiety, depression, frailty, and failure to return to work. We observed an increased risk of cognitive impairment, dementia, major bleeding, and mortality. Conversely, the incidence of cancer did not increase substantially after MI. These insights offer valuable treatment options for policymakers and physicians to develop personalized health strategies.

Conflict of Interest

The authors declare no competing interests.

Informed Consent

Not applicable due to the design of the study.

Ethics Approval

Not applicable due to the design of the study.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Authors' Contributions

Drs Dong Keon Yon and Jin-Man Cho had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. Study concept and design: Hongki Jeon, Hyeri Lee, Hwi Yang, Masoud Rahmati, Min Seo Kim, Yujin Choi, Jin-Man Cho, and Dong Keon Yon; acquisition, analysis, or interpretation of data: Hongki Jeon, Hyeri Lee, Jaeyu Park, Masoud Rahmati, Min Seo Kim, Jin-Man Cho, and Dong Keon Yon; drafting of the manuscript: Hongki Jeon, Hyeri Lee, Masoud Rahmati, Min Seo Kim, Jin-Man Cho, and Dong Keon Yon; critical revision of the manuscript for important intellectual content: all authors; and statistical analysis: Hongki Jeon, Hyeri Lee, Masoud Rahmati, Min Seo Kim, Jin-Man Cho, and Dong Keon Yon; study supervision Jin-Man Cho and Dong Keon Yon. DKY is the guarantor of this study. Hongki Jeon, Hyeri Lee, and Hwi Yang contributed equally as the first authors. Jin-Man Cho and Dong Keon Yon contributed equally as corresponding authors. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Funding

This research was funded by the BK21 FOUR program of Graduate SchooI, Kyung Hee University (KHU-20230353). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

ORCID ID

Hongki Jeon: 0000-0002-7142-958X
Hyeri Lee: 0009-0009-3132-1062
Hwi Yang: 0000-0003-1310-9921
Masoud Rahmati: 0000-0003-4792-027X
Min Seo Kim: 0000-0003-2115-7835
Yujin Choi: 0009-0002-4131-712X
Jin-Man Cho: 0000-0003-3696-3557
Dong Keon Yon: 0000-0003-1628-9948

References

1) Bauer A, Sappler N, von Stülpnagel L, Klemm M, Schreinlechner M, Wenner F, Schier J, Al Tawil A, Dolejsi T, Krasniqi A, Eiffener E, Bongarth C, Stühlinger M, Huemer M, Gori T, Wakili R, Sahin R, Schwinger R, Lutz M, Luik A, Gessler N, Clemmensen P, Linke A, Maier LS, Hinterseer M, Busch MC, Blaschke F, Sack S, Lennerz C, Licka M, Tilz RR, Ukena C, Ehrlich JR, Zabel M, Schmidt G, Mansmann U, Kääb S, Rizas KD, Massberg S. Telemedical cardiac risk assessment by implantable cardiac monitors in patients after myocardial infarction with autonomic dysfunction (SMART-MI-DZHK9): a prospective investigator-initiated, randomised, multicentre, open-label, diagnostic trial. Lancet Digit Health 2022; 4: e105-e116.
2) Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A,

Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol 2020; 76: 2982-3021.

3) Dani SS, Lone AN, Javed Z, Khan MS, Zia Khan M, Kaluski E, Virani SS, Shapiro MD, Cainzos-Achirica M, Nasir K, Khan SU. Trends in Premature Mortality From Acute Myocardial Infarction in the United States, 1999 to 2019. J Am Heart Assoc 2022; 11: e021682.

4) McManus DD, Nguyen HL, Saczynski JS, Tisminetzky M, Bourell P, Goldberg RJ. Multiple cardiovascular comorbidities and acute myocardial infarction: temporal trends (1990-2007) and impact on death rates at 30 days and 1 year. Clin Epidemiol 2012; 4: 115-123.

5) Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. Can J Cardiol 2018; 34: 575-584.

6) Lee JS, Lee YA, Shin CH, Suh DI, Lee YJ, Yon DK. Long-term health outcomes of early menarche in women: an umbrella review. QJM 2022; 115: 837-847.

7) Lee SW, Koo MJ. PRISMA 2020 statement and guidelines for systematic review and meta-analysis articles, and their underlying mathematics: Life Cycle Committee Recommendations. Life Cycle 2022; 2: e9.

8) Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, Shin JI, Won H-H. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. Eur Heart J 2021; 42: 3388-3403.

9) Zhu J, Yu X, Zheng Y, Li J, Wang Y, Lin Y, He Z, Zhao W, Chen C, Qiu K. Association of glucose-lowering medications with cardiovascular outcomes: an umbrella review and evidence map. Lancet Diabetes Endocrinol 2020; 8: 192-205.

10) Kim M, Choi Y, Lee M, Kang J, Kang SM, Lee DG, Yon DK. Maternal SARS-CoV-2 infection during pregnancy and subsequent risk of atopic dermatitis in offspring: a nationwide birth cohort study in South Korea. Br J Dermatol 2023; 190: 576-577.

11) Cho JK, Yang H, Park J, Lee H, Nguyen A, Kattih M, Rahmati M, Yon DK. Association between allergic rhinitis and despair, suicidal ideation, and suicide attempts in Korean adolescents: a nationally representative study of one million adolescents. Eur Rev Med Pharmacol Sci 2023; 27: 9248-9256.

12) Yang H, Kim MS, Rhee SY, Lee J, Cho W, Min C, Lee SW, Shin JI, Oh J, Choi Y, Lee JH, Kim H, Rahmati M, Yeo SG, Yon DK. National prevalence and socioeconomic factors associated with the acceptance of COVID-19 vaccines in South Korea: a large-scale representative study in 2021. Eur Rev Med Pharmacol Sci 2023; 27: 8943-8951.

13) Zaccone V, Falsetti L, Santoro L, Guerrieri E, Santini S, Viticchi G, Tosato M, Danese M, Miro C, Cataldi S, Gasbarrini A, Landi F, Santoliquido A, Moroncini G. Global cardiovascular risk, COVID-19 severity and post-COVID-19 syndrome: a clinical study. Eur Rev Med Pharmacol Sci 2023; 27: 12141-12152.

14) Pinheiro LSP, Ocarino JM, Madaleno FO, Verhagen E, Mello MTd, Albuquerque MR, Andrade AGP, Mata CPd, Pinto RZ, Silva A, Resende RA. Prevalence and incidence of injuries in para athletes: a systematic review with meta-analysis and GRADE recommendations. Br J Sports Med 2021; 55: 1357-1365.

15) Kim H, Kwon R, Lee H, Lee SW, Rahmati M, Koyanagi A, Smith L, Kim MS, López Sánchez GF, Elena D, Yeo SG, Shin JI, Cho W, Yon DK. Viral load dynamics and shedding kinetics of mpox infection: a systematic review and meta-analysis. J Travel Med 2023; 30: taad111.

16) Hahn JW, Lee K, Shin JI, Cho SH, Turner S, Shin JU, Yeniova A, Koyanagi A, Jacob L, Smith L, Fond G, Boyer L, Lee SW, Kwon R, Kim S, Shin YH, Rhee SY, Moon JS, Ko JS, Yon DK, Papadopoulos NG. Global Incidence and Prevalence of Eosinophilic Esophagitis, 1976-2022: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2023; 21: 3270-3284.e7.

17) Shin H, Shin H, Rahmati M, Koyanagi A, Jacob L, Smith L, Rhee SY, Kwon R, Kim MS, Kim S, Il Shin J, Min C, Cho W, Yon DK. Comparison of clinical manifestations in mpox patients living with HIV versus without HIV: A systematic review and meta-analysis. J Med Virol 2023; 95: e28713.

18) Li N, Huang Z, Zhang Y, Sun H, Wang J, Zhao J. Increased cancer risk after myocardial infarction: fact or fiction? A systemic review and meta-analysis. Cancer Manag Res 2019: 1959-1968.

19) Chen YY, Xu P, Wang Y, Song TJ, Luo N, Zhao LJ. Prevalence of and risk factors for anxiety after coronary heart disease: Systematic review and meta-analysis. Medicine 2019; 98: e16973.

20) Lian Y, Xiang J, Wang X, Kaminga AC, Chen W, Lai Z, Dai W, Yang J. Prevalence of Moderate to Severe Anxiety Symptoms among Patients with Myocardial Infarction: a Meta-Analysis. Psychiatric Quarterly 2022: 1-20.

21) Feng L, Li L, Liu W, Yang J, Wang Q, Shi L, Luo M. Prevalence of depression in myocardial infarction: a PRISMA-compliant meta-analysis. Medicine 2019; 98: e14596.

22) Yu Q, Guo D, Peng J, Wu Q, Yao Y, Ding M, Wang J. Prevalence and adverse outcomes of frailty in older patients with acute myocardial infarction after percutaneous coronary interventions: A systematic review and meta-analysis. Clin Cardiol 2023; 46: 5-12.

23) Kai SHY, Ferrières J, Rossignol M, Bouisset F, Herry J, Esquirol Y. Prevalence and determinants

of return to work after various coronary events: meta-analysis of prospective studies. Sci Rep 2022; 12: 15348.

24) Deckers K, Schievink SH, Rodriquez MM, van Oostenbrugge RJ, van Boxtel MP, Verhey FR, Köhler S. Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis. PloS one 2017; 12: e0184244.

25) McSweeney JC, Rosenfeld AG, Abel WM, Braun LT, Burke LE, Daugherty SL, Fletcher GF, Gulati M, Mehta LS, Pettey C, Reckelhoff JF. Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science: A Scientific Statement From the American Heart Association. Circulation 2016; 133: 1302-1331.

26) Park JJ, Lee M, Kim H, Park JY, Lee H, Kim HJ, Koyanagi A, Smith L, Kim MS, Rahmati M, Rhee SY, Ha Y, Lee K, Yon DK. National trends in the prevalence of hepatitis B and C in South Korea, before and during the COVID-19 pandemic (2007-2021) - a nationwide representative study. Eur Rev Med Pharmacol Sci 2023; 27: 12121-12133.

27) White DW, Raven PB. Autonomic neural control of heart rate during dynamic exercise: revisited. J Physiol 2014; 592: 2491-2500.

28) Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. J Psychosom Res 2002; 53: 897-902.

29) Kubzansky LD, Kawachi I, Weiss ST, Sparrow D. Anxiety and coronary heart disease: a synthesis of epidemiological, psychological, and experimental evidence. Ann Behav Med 1998; 20: 47-58.

30) Parvaneh S, Howe CL, Toosizadeh N, Honarvar B, Slepian MJ, Fain M, Mohler J, Najafi B. Regulation of cardiac autonomic nervous system control across frailty statuses: a systematic review. Gerontology 2015; 62: 3-15.

31) Weinstein G, Davis-Plourde K, Beiser AS, Seshadri S. Autonomic imbalance and risk of dementia and stroke: the Framingham study. Stroke 2021; 52: 2068-2076.

32) Riemer TG, Villagomez Fuentes LE, Algharably EA, Schäfer MS, Mangelsen E, Fürtig M-A, Bittner N, Bär A, Zaidi Touis L, Wachtell K. Do β-blockers cause depression? Systematic review and meta-analysis of psychiatric adverse events during β-blocker therapy. Hypertension 2021; 77: 1539-1548.

33) Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. β-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA 2002; 288: 351-357.

34) Awada Z, Abboud R, Nasr S. Risk of Serious Bleeding with Antiplatelet Therapy for Secondary Prevention Post Ischemic Stroke in Middle East Population. Cureus 2019; 11: e4942.

35) Faridi KF, Tamez H, Strom JB, Song Y, Butala NM, Shen C, Secemsky EA, Mauri L, Curtis JP, Gibson CM. Use of administrative claims data to estimate treatment effects for 30 versus 12 months of dual antiplatelet therapy after percutaneous coronary intervention: findings from the EXTEND-DAPT study. Circulation 2020; 142: 306-308.

36) Kang K, Gholizadeh L, Inglis SC, Han HR. Interventions that improve health-related quality of life in patients with myocardial infarction. Qual Life Res 2016; 25: 2725-2737.

37) Lutz AH, Forman DE. Cardiac rehabilitation in older adults: Apropos yet significantly underutilized. Prog Cardiovasc Dis 2022; 70: 94-101.

38) Jacobsen AP, Raber I, McCarthy CP, Blumenthal RS, Bhatt DL, Cusack RW, Serruys P, Wijns W, McEvoy JW. Lifelong Aspirin for All in the Secondary Prevention of Chronic Coronary Syndrome: Still Sacrosanct or Is Reappraisal Warranted? Circulation 2020; 142: 1579-1590.

39) McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, Reid CM, Lockery JE, Kirpach B, Storey E, Shah RC, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Johnston CI, Ryan J, Radziszewska B, Jelinek M, Malik M, Eaton CB, Brauer D, Cloud G, Wood EM, Mahady SE, Satterfield S, Grimm R, Murray AM; ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018; 379: 1509-1518.

40) Loud JT, Murphy J. Cancer Screening and Early Detection in the 21(st) Century. Semin Oncol Nurs 2017; 33: 121-128.