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Meta-analysis of prevalence and prognosis of AHF in patients admitted with myocardial infarction: role of invasive management in determining patients' outcomes

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Abstract. – OBJECTIVE: This meta-analysis aimed to reveal the prevalence and prognosis of heart failure in myocardial patients. This study further sought to explore the role of treatment in determining outcomes.

MATERIALS AND METHODS: This systematic analysis was performed on the principles of the pre-designed protocol of meta-analysis and systematic reviews statement. Online search articles were accessed for analysis. Studies from January 2012 to August 2020 were considered to identify the prognosis and prevalence of acute heart failure and myocardial infarction. Cochran's Q-test and I^2-test were used to measure heterogeneity across the studies. Meta-regression was also performed to identify the potential source of heterogeneity.

RESULTS: For the final analysis, 30 studies were included. No significant publication bias was reported on the funnel plot. However, a 0.462 value was reported for short-term mortality, whereas 0.274 was reported for the long term while performing Egger's tests. Meanwhile, the Begg test showed a value of 0.274 for publication bias. However, an asymmetrical funnel plot suggested potential publication bias.

CONCLUSIONS: After adjustment of clinical and cardiovascular baseline, significant results related to the impact of sex differences on mortality could be obtained. Disease prognosis may be affected by co-morbidities, especially diabetes Mellitus, kidney disease, hypertension, and COPD worsening the situation of patients.

Key Words:
Meta-analysis, Acute heart failure, Myocardial infarction.

Introduction

Heart failure is a frequent complication of myocardial infarction. This complication may occur early or late in life and can be resolved with time[1]. Despite improving acute cardiac care, acute myocardial infarction is the leading cause of mortality worldwide in both male and female populations[2]. Compared to men, women reported a high frequency of long-term mortality and adverse events following ST-segment elevation myocardial infarction (STEMI)[3]. Advanced age and co-morbidities, especially diabetes mellitus and hypertension, are one of the major contributors to female mortality[4,5]. Furthermore, scholars6 revealed an association between a lower rate of medical therapies and revascularization with poor prognosis for women with STEMI. The prevalence of heart failure events in myocardial infarction patients varies in various studies[4-7]. In the past, 14% to 36% of cases of heart failure were reported after myocardial infarction[7]. Incidents of heart failure can be reported at the time of admission, but most cases develop heart failure during hospitalization. From 1992 to 1996, the study reported 4% of cases with symptoms of HF at the time of admission, while 39% developed during hospitalization[8]. A pooled study of 7 randomized controlled trials reported 1.74 prognoses of HF at the time of admission, which was increased up to 2.34 times in 30 days of mortality analysis[9]. This meta-analysis aimed to reveal the prevalence and prognosis of heart failure in myocardial patients. This study further aimed to explore the role of treatment in determining outcomes.

Materials and Methods

This systematic analysis was performed on the principles of the pre-designed protocol of

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meta-analysis and systematic reviews statement [Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)][10]. The study was also registered on PROSPERO (reference number: 421046).

Comprehensive research on PUBMED, EMBASE, and Cochrane Library was conducted. Studies from January 2012 to August 2020 were considered to identify the prognosis and prevalence of acute heart failure and myocardial infarction. Key variables like sex differences regarding short and long-term mortality prevalence in STEMI patients were addressed for this research. Studies related to non-ST-segment elevation myocardial infarction and acute myocardial infarction were also included. Both clinical trials and observational studies were eligible for this research[11]. Two reviewers independently performed abstract research to find eligible articles containing information on two concepts: acute myocardial infarction and acute heart failure or heart failure. We further extract those articles containing three search terms: gender, mortality, and myocardial infarction. Keywords like female, male, gender differences, cardiovascular death, hospital mortality, long-term mortality, all-cause mortality, primary PCI, primary percutaneous coronary intervention, rehospitalization, etc., were searched to identify the relevant studies. However, no language restrictions or age limits were set. A second full-text screening for text eligibility was performed by two other reviewers. The following criteria were set for the inclusion of studies: i) studies that provide enough details related to risks and events; ii) mortality data specific to myocardial infarction patients[12]. All the studies with irrelevant titles, abstracts, text not involving information on acute heart failure, commentary, case reports, or pooled studies were excluded. Studies containing pregnant participants and seriously ill patients were also excluded. Duplicate researchable is also excluded. The third reviewer evaluated disagreements during the study period and managed by consensus.

Excel sheets extracted demographic information, region, study population, sample size, enrollment time, study type, endpoints, and follow-up duration. Newcastle-Ottawa scale[13] was used to assess the quality of the study, including study population, study design, outcomes, response rate, and one point for each item. A quality score was classified according to the maximum of 1 point for each item.

Statistical Analysis

Primary outcomes were the prognosis of heart failure in myocardial patients. Risk ratios and 95% confidence interval were primarily used for presenting sex differences in heart failure mortality after myocardial infarction. The random effect model of DerSimonian and Laird was used to combine the data with inverse variance weighting. Clinical and statistical heterogeneity was assessed by using the random-effect model. Unadjusted RRs were used to evaluate the long and short-term all-cause mortality using a raw number of deaths and risk of deaths, while adjusted residual sum of squares (RRs) were used to describe the mortality if mentioned in the included studies. The RRs was also used to calculate the in-hospital and 30-day mortality.

Meanwhile, to analyze the heterogeneity across studies, Cochran's Q-test and I^2-test were performed. The p-value <0.1 or I^2>50% were considered significant. Meta-regression analysis was also computed to investigate the source of heterogeneity. These sources were described in terms of diabetes differences. Differences between the hypertension rate, hyperlipidemia, rate of smoking, prior MI, and prior percutaneous coronary intervention (PCI) were also measured to evaluate the heterogeneity sources. For this study, stratified analysis was performed by dividing studies into subgroups based on the Newcastle-Ottawa scale scores (>7 points or ≤7 points) to assess the potential sources of heterogeneity. To mention the publication bias, this study used Egger's regression asymmetry test, and a funnel plot was used. Sensitivity analysis was also performed by restricting the high-quality studies. Statistical analyses were performed by using STATA V.15.0 (StataCorp LP, Stata Statistical Software, TX, USA). Significant statistical differences were represented by a two-sided p-value<0.05.

Results

For analysis a total of 2,611 studies were identified for review. Out of these, 2,495 were excluded after full-text screening. A total of 116 fulfilled the inclusion criteria but 86 out of them were excluded due to enrolment starting earlier than a decade ago. A total of 30 studies were finally included in the study (Figure 1).

Of these 30 studies[14-43], thirteen[15-19,21,23,25,31,33,36,40,41] were prospective with major endpoints of mortality, all-cause mortality, cardiovascular death, STEMI, AMI, and 30 days readmission due to heart failure. For this analysis total of 128,585 patients were diagnosed with

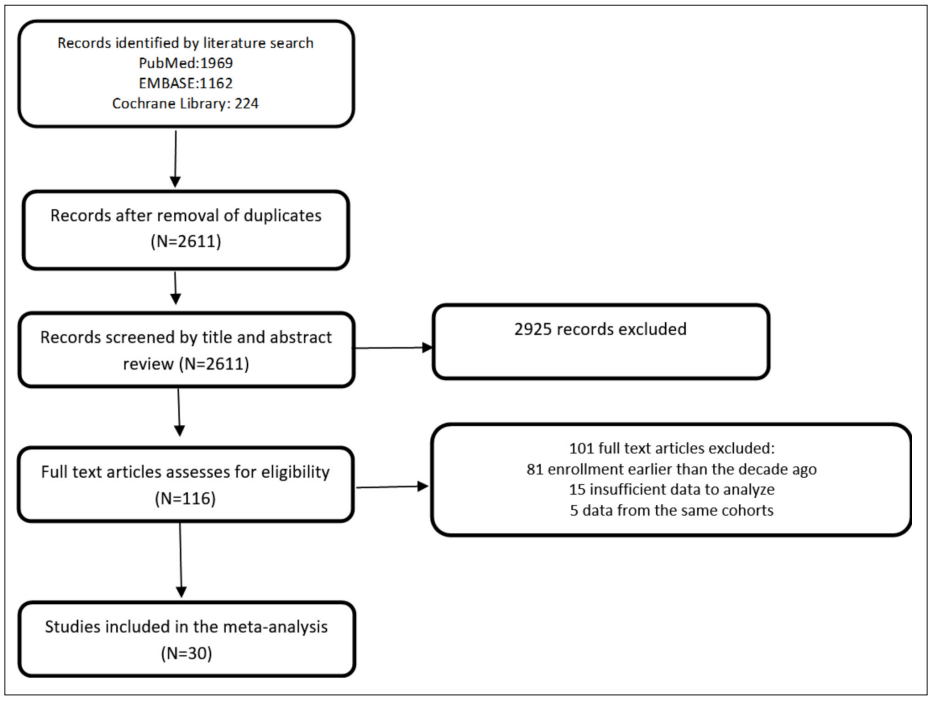

Figure 1. Prisma flow chart of selected studies.

STEMI, of which 31,706 (24.7%). In the majority of studies, females were elderly and reported high cases of diabetes mellitus than males. Hypertension and hyperlipidemia were also frequently observed in females. On the other hand, greater proportions of males were smokers and had prior PCI or MI. Unadjusted short-term mortality was mentioned in 13 studies[15-19, 21,23,25,31,33,36,40,41]. Out of these, seven studies[18,22,27,28,30,32,34] reported 30 days of hospital mortality, while the rest 6[20,24,26,29,36,38,42] were focused on heart failure developed in the hospital. These studies revealed that women are more prone to all causes of mortality in 9.1% of cases, while males reported a 4.6% ratio. A complete subgroup analysis was reported in Table I.

In Table II, statistical analysis was performed on risk factors associated with readmission. From this analysis, findings revealed the significant heterogeneity of results. Diabetes, COPD, kidney disease, and HF were the major reasons for readmission after MI. A total of 2,873 cases of short-term mortality were noticed in this meta-analysis. Nine studies[27,29,33,35,37,38,40,41,43] reported adjusted RR ratios related to MI mortality. Adjusted analysis revealed a significant mortality ratio in the female population (RR, 1.24; 95% CI: 1.11 to 1.38, $p<0.001$, $I^2=39.6\%$). The non-American region reported a lower risk of readmission after MI (CI: 95%; 0.11-0.15) (Figure 2). Overall, 77.9% heterogeneity was reported among studies. No significant publication bias was reported on the funnel plot. However, a 0.462 value was reported for short-term mortality, whereas 0.274 was reported for the long term while performing Egger's tests.

Meanwhile, the Begg test shows a value of 0.274 for publication bias. Nonetheless, an asymmetrical funnel plot suggested potential publication bias (Figure 3).

Discussion

Heart failure is a major reason for myocardial infarction. This complication may occur early or late in life and can be resolved with time[1]. Poor prognosis and a high risk of heart failure have been seen in elderly patients[44]. This systematic review and meta-analysis demonstrate that female STEMI patients had a higher risk of short-term heart failure mortality than males. After adjustment of cardiovascular risk factors and clinical profile, a significant reduction was observed in sex differences, and females have similar long-term mortality to males. The results of this meta-analysis were concurrent with the previously published meta-analysis[3,45]. After acute coronary

Table I. Subgroup analysis[13].

	RR	95% CI	*p*-value	I^2
Unadjusted Model				
Newcastle-Ottawa scale				
>7	1.90	1.73 - 2.09	0.018	63.4%
≤7 points	1.52	1.20 - 1.93	0.026	58.1%
Short-term all-cause mortality				
Impact of sex on in-hospital	1.71	1.27 - 2.31	<0.001	86.4%
Impact of sex on 30 days mortality	1.81	1.62 - 2.02	<0.001	56.6%
PCI/CABG for STEMI	1.45	1.05 - 2.00	0.026	39.5%
Long-term all-cause mortality				
Sex difference	1.23	0.89 - 1.69	0.206	77.5%
PCI/CABG	1.28	0.95 - 1.73	0.108	0.0%
The adjusted risk of mortality at long term follow-up	1.11	0.42 - 1.80	0.670	74.5%
Sensitivity analysis of short-term mortality	1.75	1.54 - 1.99	<0.001	82.9%
Sensitivity analysis of long-term mortality	1.50	1.23 - 1.83	<0.001	40.9%

Table II. Risk factors associated with readmission[12].

Risk factors of 30 days readmission	Pool odd ratios 95% CI	I^2	*p*-value
Female sex	1.17 (1.15 - 1.20)	0%	0.594
Cardiogenic shock	1.24 (0.81 -1.91)	88%	0.004
Hypertension	1.03 (0.93 - 1.15)	37.7%	0.201
Previous MI	1.22 (0.98 - 1.52)	98%	0
Diabetes mellitus	1.23 (1.18 - 1.28)	51%	0.069
COPD	1.20 (1.11 - 1.30)	82.1%	0
Length of stay at index hospitalization	1.21 (0.81 - 1.82)	88.8%	0.003
Heart failure	1.32 (1.20 - 1.44)	91.8%	0
Blood disease	1.16 (1.09 - 1.23)	83%	0.003
Kidney Disease	1.53 (1.29 - 1.81)	88%	0

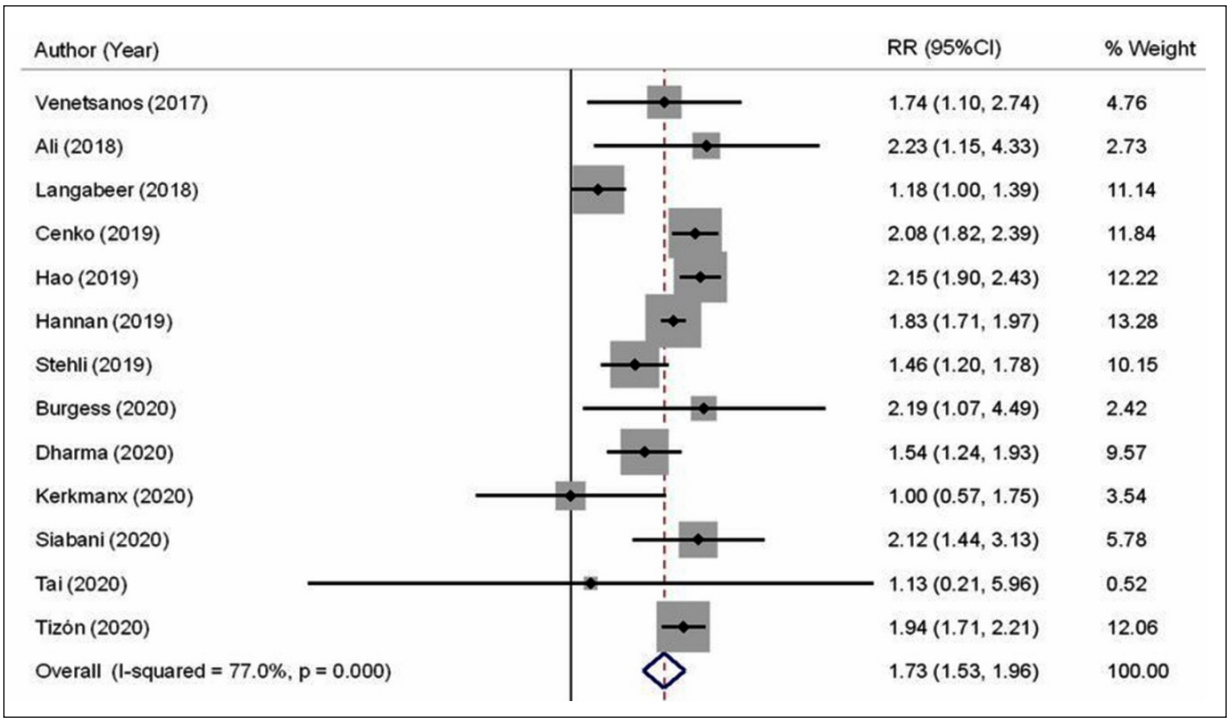

Figure 2. Summary of RR square effect ratios and weight.

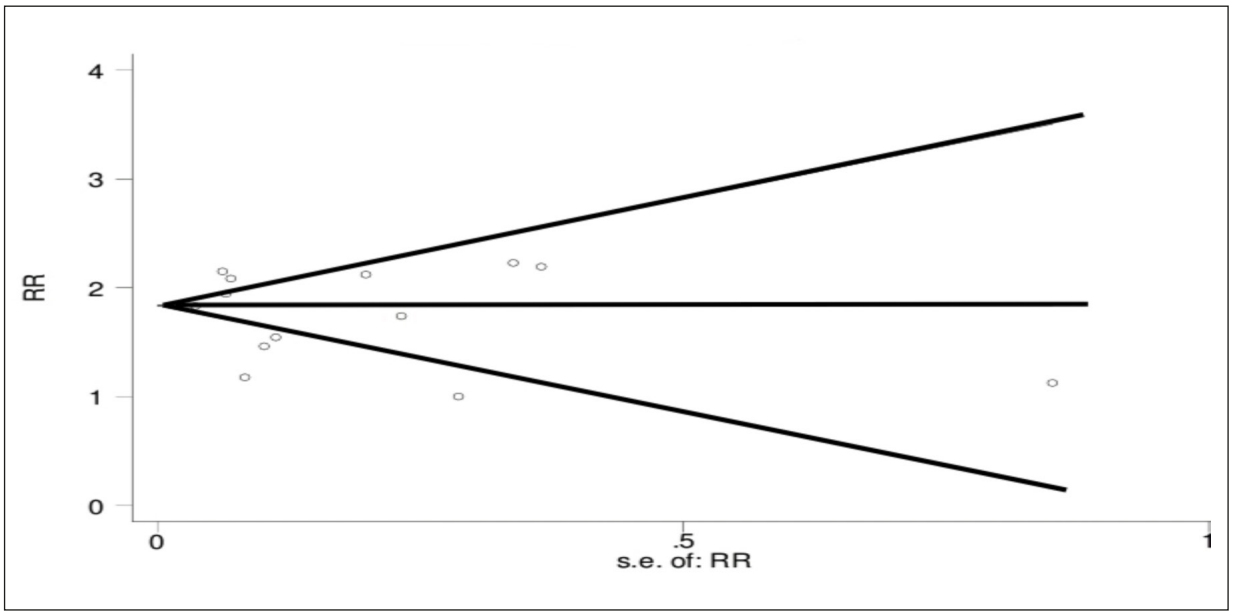

Figure 3. Begg plot of publication bias.

syndrome (ACS) high risk of short-term mortality was observed in previous studies[40,43]. However, long-term mortality among female patients remains debatable. Some studies[39,41,46] highlight that the female population suffering from STEMI had a higher one-year mortality ratio than men[46], while some show contradictory results[39,41]. In the current meta-analysis, high or low-quality studies with small and large sample sizes show similar results. Adjusted analysis revealed a non-significant increase in long-term mortality, while sensitivity analysis found a significant association between long-term mortality and female sex after removing one study[47] from adjusted analyses. In the past, significant sex differences among acute myocardial patients were confirmed. Adjusted analysis of cardiovascular risk factors highlights the impact of sex differences on mortality. Tang et al[47] revealed that elderly STEMI female patients have a high burden of co-morbidities contributing to heart failure after myocardial infarction. In the current meta-analysis, older female patients had diabetes and hypertension. Sex-specific studies[48,49] found potent co-morbidities ratio and risk factors in women[47]. Smoking status, diabetes, and hypertension enhanced the probability of cardiac events in female STEMI patients more than in males.

Predicting risk factors and identifying readmission reasons after acute myocardial infarction enables reducing the burden on the healthcare department[50]. Initially, patients reported chest pain and heart failure, which required 30 days of readmission. This meta-analysis revealed a 12% readmission prevalence after acute myocardial infarction, while Dharmarajan et al[51] reported 19.9% of cases within 30 days and almost 67.6% of readmissions occurring within 15 days of discharge. Current study subgroup analyses indicated a stable readmission ratio in the American population >10,000 sizes. The unplanned readmission rate could have been higher in the literature we included. Heterogeneity in the current meta-analysis it was observed due to differences in age size, sex, diagnosis technique, and study type. Due to data limitations, this meta-analysis conducted subgroup analysis only on variables including region, quality of size, and sample size. The pooled prevalence of 30-day readmissions in influence analysis did not fluctuate or affect the overall readmission rate.

Kidney disease, diabetes mellitus, COPD, and heart failure were the major predictor factors of readmission. The current meta-analysis revealed a positive association of chronic kidney disease with hypertension and dyslipidemia, which eventually results in atherosclerosis and endothelial dysfunction. These two were observed as independent risk factors for acute myocardial patients[52]. Gender was observed as the second independent risk factor. Past research[53] revealed a high readmission ratio in young females suffering from acute MI due to different pathophysiological and clinical characteristics.

Women experienced more myocardial ischemia than coronary artery obstruction[54]. Patients with co-morbidity of diabetes mellitus had two times more risks of heart failure[54]. Renal insufficiency enhances the risk of cardiac events and unfavorable prognosis[55]. Hawkins et al[56] observed more increased mortality with co-morbidity of COPD. Previous studies[14,30] demonstrate declined ratio of revascularization in those who received interventional procedures, especially those who underwent PCI.

Some previous studies[57,58] reported an 8% readmission rate after PCI, while Pelletier et al study showed that 17.5% of cases who underwent PCI reported readmission after myocardial infarction. This ratio is greater than our meta-analysis. Long-term mortality and morbidity can be decreased by PCI with improvement in prognosis[59]. Delayed presentations of female cases were the main reason for sex differences. Despite great advancements in medical emergency medical services and timely revascularization, recent studies[60,61] reported that women had more ischemic time, door-to-balloon time, and door-to-needle time than men. After developing MI symptoms, women continue to have more time to seek medical attention, and delayed treatment timing enhances the risk of mortality[62]. No signs of chest pain were reported in the female gender, which causes obstacles in decision-making to pursue less aggressive care[63,64]. Some studies[21,25] of this meta-analysis enrolled patients undergoing PCI, which might be the potential source of heterogeneity. The results of the present study are comparable with the previous meta-analysis of Pancholy et al[3], in which he observed significant sex differences among STEMI patients treated with PCI. In his meta-analysis, he revealed that the probability of hospital mortality raised along with a significant reduction of one-year mortality in women when using adjusted RR ratios. More than 90% of studies in the current meta-analysis used PCI treatment for their patients. However, bleeding, mechanical complications, and acute heart failure were highly observed in the female population. Three included studies[15,21,31] revealed a high risk of bleeding in women, Khan et al[63] study revealed that women are at high risk of de novo heart failure after STEMI, and those who developed de novo heart failure had worse survival ratios than men. Mechanical complications that require surgical intervention are also common in the female population.

Limitations

This meta-analysis has certain limitations. Firstly, all the chosen articles had different risk variables and inconsistent definitions, which caused obstacles in combining them in the meta-analysis. In addition, each study's age group was different, leading to overlapping. Secondly, the heterogeneity between studies came from age, study period, diagnosis, and population. Moreover, not all studies reported similar cofounders for adjusted analysis, and not all reported adjusted RRs. A random effect model was used for significant heterogeneity to overcome this issue. Thirdly majority of the studies were observational. Only four to five were clinical trials[15,21,23,27,31]. There may be implicit confounding bias in this meta-analysis's observational study design. However, no correction bias was attempted. During the COVID-19 pandemic, the prognosis of heart failure was increased due to the impact of COVID-19 infection; that's why we exclude those studies.

Conclusions

In conclusion, pool results revealed that women had a high prognosis of heart failure after myocardial infarction than males. After adjustment of clinical and cardiovascular baseline, significant results related to the impact of sex differences on mortality could be obtained. Disease prognosis may be affected by co-morbidities, especially diabetes mellitus, kidney disease, hypertension, and COPD worsening the situation of patients.

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Conflict of Interest
No conflict of interest.

Authors' Contribution
W.O.A and H.M.A. conceived and designed the study, W.K.Z.A and M.A.A conducted research, provided research materials, and collected and organized data. A.B.A, A.G.A, and M.A.A analyzed and interpreted data and provide logistics. H.B.S, M.M.A and L.A.A wrote the initial and final draft of the article, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Ethics Approval and Informed Consent
Not applicable.

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