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Gender Disparities and Multimorbidity among Hospitalized Patients

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Abstract:

Objective: To assess gender disparity in the prevalence of multimorbidity and outcomes among hospitalized patients with acute myocardial infarction (AMI), acute decompensated heart failure (ADHF), or pneumonia.

Patients and Methods: We conducted a retrospective study of adults hospitalized for AMI, ADHF, or pneumonia from January 1, 1995 through August 31, 2015. Patients were selected using ICD-9 codes. Comorbidities were chosen from the twenty chronic conditions, specified by the Office of the Assistant Secretary for Health. Logistic regression analysis was conducted adjusting for multiple confounders.

Results: We evaluated 12,265 patients with ADHF, 15,777 patients with AMI and 12,929 patients with pneumonia. Prevalence of comorbidities was significantly different between men and women in all 3 conditions. After adjusting for age, length of stay, multi-comorbidities, and residence, there was no significant difference in 30 day mortality between men and women in AMI or ADHF, but men with pneumonia had slightly higher 30 day mortality with an odds ratio (OR) of 1.19 (95% CI 1.06 to 1.34). There was no significant difference in 30 day readmission between men and women with AMI or pneumonia, but women with ADHF were slightly more likely to be readmitted within 30 days with OR 0.90 (95% CI 0.82 to 0.99).

Conclusion: Gender differences in the distribution of comorbidities exist in patients hospitalized with AMI, ADHF, and pneumonia. However, there is minimal clinically meaningful impact of these differences on outcomes. Efforts to address gender difference may need to be diverted towards targeting overall population health, reducing race/ethnicity disparity, and improving access to care.

Article summary:

Strengths and limitations of this study:

- The strengths of this study include the large sample size, multivariable adjustment and sensitivity analyses to assess robustness of findings.
- A limitation of this study is including all patients that were hospitalized in a single regional tertiary center; these patients were from several different states and some from were from other countries. We might have under estimated the mortality or readmission rates if these patients were readmitted to a different hospital closer to their residency place after discharge.
- Another limitation is that the majority of our included patients were white; our results may not be generalizable to people from other races.

Introduction:

Acute decompensated heart failure (ADHF), acute myocardial infarction (AMI), and pneumonia are among the most common causes of hospitalization in the United States, with more than 2.5 million hospitalizations per year, and estimated annual hospital cost of $31.3 billion.[1,2] Hospitalized patients with ADHF, AMI, or pneumonia are at high risk of death and readmission at 30 days after index hospitalization.[1,2] In the United States, 15.1% of patients with acute myocardial infarction (AMI), 11.4% of patients with ADHF, and 11.3% patients with pneumonia die within 30 days after hospitalization for respective disorders.[3,4] Likewise, 24.8%, 19.9% and 18.3% of patients hospitalized for ADHF, AMI, and pneumonia respectively are readmitted within 30 days of the first hospitalization.[5] Risk standardized 30-day mortality and readmission rates are quality performance measures for AMI, ADHF, and pneumonia.[6] However, these outcomes vary between males and females.[5]

In the past several decades, gender disparities in clinical outcomes of hospitalized patients with different diseases have been investigated.[7,8] Several studies suggested gender differences in clinical outcomes for patients with AMI, ADHF and Pneumonia.[9-12] Females have worse outcomes for pneumonia than males, with adjusted risk ratio of 1.15 for 28 days mortality.[13] Women with acute coronary syndromes were at a higher risk for unadjusted in-hospital death (5.6% vs. 4.3%)[8] and they are more likely to have adverse outcomes (myocardial infarction, stroke and readmission) compared to men (odds ratio 1.24, 95% CI 1.14 to 1.34).[14]

Although no gender differences were found in outcomes in patients with ADHF, there were significant gender differences in the clinical characteristics at presentation including age and comorbidities.[9]

Multimorbidity, defined as existence of two or more disorders in an individual patient, has become a public health issue of increasing magnitude. Around one third of all Americans have multimorbidity (31.5%), and the rate is expected to increase with time.[15] Multimorbidity is associated with premature death, propensity for over investigation, duplicate tests, medication non-adherence, polypharmacy with increased risk for drug adverse events, and a decline in functional status.[15] Mutlimorbidity itself may have gender disparities. The US National Health and Nutrition Examination Survey (NHANES) when looking at persons 65 years and older found that 83% of women compared to 65% men with coronary artery disease had one of the four comorbid conditions (arthritis, chronic lower respiratory tract disease , diabetes mellitus, and stroke).[16] European data suggest a similar difference in prevalence of multimorbidity between men and women.[17]

Although the above data provide sex-related differences in the prevalence of multimorbidity in specific patient population, the disparity in rates of occurrence of comorbid conditions and their impact on early clinical outcome have not been reported by gender for broader hospitalized patients with ADHF, AMI, and pneumonia.

To address this gap in knowledge, we evaluated gender-specific differences in prevalence of individual and multiple comorbid conditions in a large hospital-based patient population with ADHF, AMI, and pneumonia. Furthermore, we determined whether the

presence of individual or multimorbidity impacts 30-day mortality or readmission by gender independent of demographic and social characteristics.

Methods:

Study design and Population sample:

This is a retrospective study of patients aged ≥18 years hospitalized for ADHF, AMI, and pneumonia at Mayo Clinic, Rochester, Minnesota, from January 1, 1995 to August 31, 2015.

We included first hospitalization in the analysis when a patient had multiple repeat hospitalizations for the same condition. The data were extracted by dedicated abstraction personnel using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (supplementary tables 1-3). We abstracted data-related to age, gender, race, zip code, insurance, principal discharge diagnosis, secondary diagnoses, length of hospital stay, death, and readmission by date. The diagnoses of AMI, ADHF, and pneumonia were based on physician provider as documented in clinical notes. Patients who refused participation in clinical research were excluded. The study was approved by the Mayo Clinic Institutional Review Board.

Patient and Public Involvement: patients and public were not involved.

Measure of multi-comorbidities:

Comorbidities were chosen from twenty chronic conditions (Supplementary Table 4) specified by the Office of the Assistant Secretary for Health (OASH) [18] using ICD-9-CM codes (Supplementary table 5). Multi-comorbidities were categorized into four groups based on the number of existing chronic conditions: less than 2 comorbidities, 2 comorbidities, 3 comorbidities, and 4 or more comorbidities.

We did not use composite morbidity index such as Charlson, since it needed to be modified for this study. For example, we did not count coronary artery disease (CAD) as

one of the comorbidities for patients hospitalized for AMI, the same for congestive heart failure for patients with ADHF.

We excluded 4-comorbid conditions (autism, schizophrenia, hepatitis, and HIV) from the analysis because of very low frequency of occurrence (<1%)..

Measures of outcomes:

The primary outcomes were prevalence of comorbidities in men and women, 30 day mortality, defined as 30 days from the day of admission with one of the primary diagnosis, and 30 day readmission for any cause since discharge date.

Statistical analysis:

Baseline characteristic data were summarized as mean and standard deviation for continuous variables and as for categorical variables. Prevalence of comorbidities and the number of multi-morbidities in men and women were compared using Chi^2 tests. Gender differences in 30 day mortality and 30 day readmission were presented as odds ratio. Logistic regression models were developed to estimate the risk of outcomes of interest while controlling for various confounders (age, length of stay, Olmsted county residency, and number of comorbidities). Results are reported as odds ratios and 95% confidence intervals (CI). A two-tailed P value <0.05 was considered as statistically significant and all analyses were performed using STATA 14.0 (StataCorp, College Station, Texas).

Results:

40,971 patients were included during the study period, 12,265 with ADHF, 15,777 with AMI, and 12,929 with pneumonia. There were more men in all three conditions, and men were older. (Table 1)

The prevalence of each comorbidity in men and women were reported in Table 1. The majority of deaths due to AMI occurred in the first 10 days; whereas this trend was not evidence for pneumonia or ADHF (Supplementary figures 1-3). The majority of readmissions for all three conditions occurred in the first 15 days (Supplementary figures 4-6).

Summary of outcomes

ADHF:

12,265 patients were hospitalized with ADHF within the study period, 7,010 men and 5,255 women. Women were older with a mean age of 75.4 years compared to 72.3 years in men. 85.75% of both men and women were Caucasian. 71.94 % of men had multi-comorbidities compared to 69.99 % of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 0.94 (95% CI: 0.82, 1.07), OR for 30 day readmission 0.90 (95% CI: 0.82, 0.99). (Table 2), (Figure 1)

AMI:

Of the 15,777 patients hospitalized with AMI 10,280 were men and 5,497 were women. Women were older, with a mean age of 73 years compared to 66.5 years in men. 86.78%

of patients were Caucasian (87% of men and 86% in women) (Table 2). 46.73 % of men had multi-comorbidities compared to 52.17 % of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 0.98 (95% CI: 0.86, 1.11), OR for 30 day readmission 0.90 (95% CI: 0.79, 1.04). (Table 2) (Figure 1)

Pneumonia:

Of the 12,929 patients hospitalized with pneumonia within the study period, three were 7,073 men and 5,856 women. Women were older with a mean age of 70.8 compared to 69.2 years in men. 85% of both men and women were Caucasian. 58.89% of men had multi-comorbidities compared to 55.79% of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 1.19 (95% CI 1.06, 1.34), OR for 30 day readmission 1.10 (95% CI 0.99, 1.23). (Table 2) (Figure 1)

Sensitivity analysis:

To determine the contemporary status of gender disparities and comorbidities, we conducted a sensitivity analysis focusing on patients who were admitted in the last 5 years. The results were overall consistent with the main analysis, except for 30 day mortality for pneumonia (which became nonsignificant between men and women whereas mortality was marginally higher in men, in the original analysis). (Supplementary table 6).

We conducted another sensitivity analysis, looking for 15 day mortality and readmission. There were no statistically significant differences in 15 day readmission between men and women in all 3 conditions. 15 day mortality was marginally higher for pneumonia in men OR: 1.15 (95% CI: 1.00 to 1.33) but not statistically significant different in AMI or ADHF (Supplementary table 7).

Discussion:

This study suggests that comorbidities are distributed differently between men and women hospitalized for ADHF, AMI and pneumonia. Despite a fairly large sample size, this study showed that gender differences appear to have minimal meaningful impact on outcomes.

In AMI, women are known to less commonly report chest pain or discomfort compared with men, this may lead to gender differences in outcomes of AMI.[19] However, in our study, the gender difference in 30-day mortality could be explained by the age difference, women were 6.5 years older in average. After adjusting for residency location and number of comorbidities, age had a significant impact on 30 day mortality, but not gender or multi-comorbidities. On the other hand, the only factor that had a significant association with 30 day readmission was multi-comorbidities.

In ADHF, men had significantly lower 30 day readmission rate compared to women, while they did not have a significant difference in 30 day mortality. A sensitivity analysis including only patients for the last 5 years, showed similar results. Multi-comorbidity did not have a significant effect on 30 day mortality or readmission. This might be explained by difference in symptoms presentations, or difference in access to medical care between

men and women. For example, men used to have higher invasive cardiac procedures than women in a previously published study.[20]

Men with pneumonia had significantly lower 30 day mortality compared to women, but no significant difference in 30 day readmission. Multi- comorbidities had a significant effect on 30 day readmission in men but not in women.

Comparison with existing literature

Our findings in AMI were consistent with previously published studies[11,21] that showed a higher 30 day mortality rate in women verses men, but no significant difference after adjustment for other variables. In these studies, they include elderly patients only (> 65 years old) while we had no age restriction, but yet, in all of these studies, women were older, and had differences in comorbidities compared to men. In ADHF, our results were consistent with a previously published study that used ADHERE (Acute Decompensated Heart Failure National Registry) between 2001 and 2004[9], in both studies there was no significant difference in in-hospital mortality between men and women.

In pneumonia, our study showed that men have worse outcomes than women, unlike a previous study[13] that found that women have worse outcomes for community-acquired pneumonia with 28-day mortality odds ratio of 1.15 (95% CI 1.02–1.30). Howver, our study included all types of pneumonia, and it was consistent with another study that used the Medicare database and showed worse outcomes in men[22].

Limitations and strengths

A limitation of this study is that we used ICD-9 codes for identifying patients. It was not feasible to review charts for such a large number of patients; and therefore, we had to depend on administrative and billing codes. New research using the recent ICD-10

coding is needed to study the consistency of prevalence and implication of comorbidities on early outcomes in hospitalized patients. Another limitation is that we included all patients that were hospitalized in a single regional tertiary center; these patients were from several different states and some from were from other countries. We might have under estimated the mortality or readmission rates if these patients were readmitted to a different hospital closer to their residency place after discharge. Making this less concerning is the fact that we found, gender to be an independent variable from residency place; in addition, we adjusted for residency place (Olmsted County where the hospital is vs. non Olmsted County). Another limitation is that the majority of our included patients were white; our results may not be generalizable to people from other races. The strengths of this study include the large sample size, multivariable adjustment and sensitivity analyses to assess robustness of findings.

Clinical and policy implication:

Although this study showed that women hospitalized for ADHF had higher 30 day readmission rate, the absolute risk was small with a number needed to harm of 88 patients (95% CI: 48, 445). For pneumonia, women had lower mortality, with a number needed to harm of 61 patients (95% CI: 36, 202). With this minimal clinically meaningful impact of these differences on the early outcomes of these three important conditions; efforts to address gender difference may need to be diverted towards targeting overall population health, where outcomes of these conditions are still suboptimal in both genders, or towards reducing race/ethnicity disparity, or improving access to care differences.

Conclusion:

Gender disparities interact with comorbidities and impact mortality and readmission. However, this effect varies according to the conditions, seems to be unpredictable and has a minimal meaningful impact on outcomes.

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Contributors: MA conception and design of the study, data collection, data analysis, interpreted results, drafted and revised manuscript; ZW data analysis, manuscript revision and approval of final draft; MHM contributed to study design, manuscript development, approval of final draft; MY: developed the idea for the study, interpreted results, revised manuscript, approval of final draft.

Competing interests: None declared

Ethics approval: Mayo Clinic Institutional Review Committee (IRB).

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Data sharing statement: No additional data are available.

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Legends:

Table 1: Baseline characteristics

Table 2: Adjusted outcomes

Figure 1: Adjusted outcomes 30 day mortality and 30 day readmission in med vs. women.

Table 1: Baseline characteristics

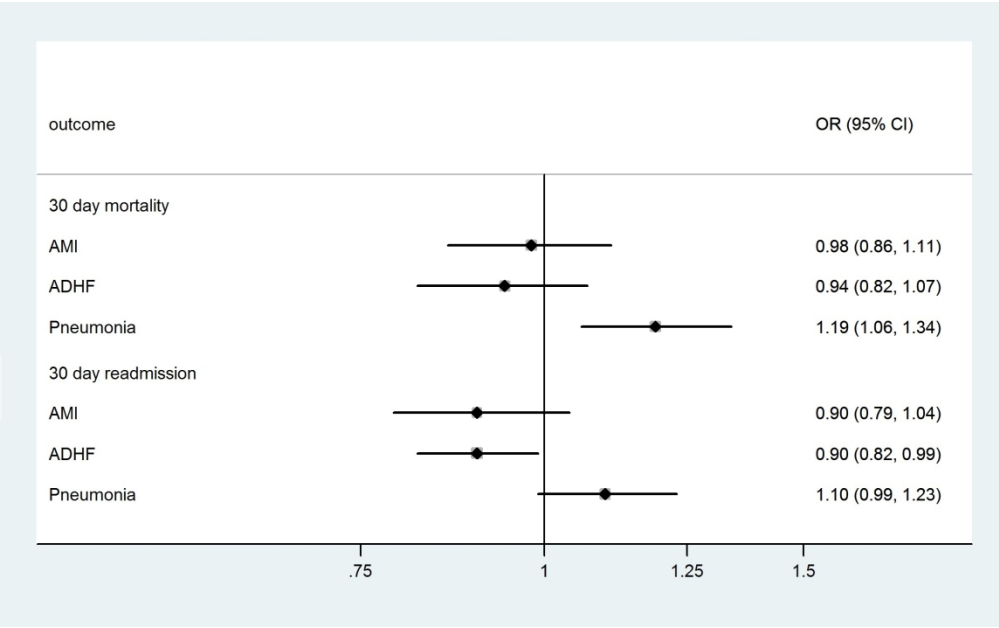
	AMI = 15,777			ADHF =12,265			Pneumonia = 12,929		
	Men 65%	Women 35%	P value	Men 57%	Women 43%	P value	Men 55%	Women 45%	P value
Age (SD)	66.5 (13.3)	73 (13.3)	<0.001	72.3 (13)	75.4 (13.9)	<0.001	69.2 (16.8)	70.8 (17.7)	<0.001
Race %									
Non-white	12.74%	14.12%	0.015	14.25%	14.25%	0.997	15.65%	14.70%	0.14
White	87.26%	85.88%		85.75%	85.75%		84.35%	85.30%	
Comorbidity									
Arthritis	3.37%	5.57%	0.06	4.35%	6.95%	<0.001	4.28%	7.26%	<0.001
Asthma	2.42%	3.89%	<0.001	2.81%	5.25%	<0.001	5.09%	10.31%	<0.001
Dementia	1.73%	3.29%	<0.001	2.65%	4.17%	<0.001	6.9%	8.52%	0.001
Depression	4.4%	6.8%	<0.001	6.28%	9.12%	<0.001	8.64%	12.93%	<0.001
Hypertension	57.64%	65.69%	<0.001	56.52%	62.11%	<0.001	43.91%	48.80%	<0.001
Osteoporosis	0.4%	4.73%	<0.001	0.97%	7.16%	<0.001	2.09%	9.00%	<0.001
Cancer	8.14%	6.95%	0.01	13.42%	11.91%	0.01	25.93%	17.81%	<0.001
Drug abuse	4.15%	1.47%	<0.001	3.65%	0.97%	<0.001	4.54%	2.36%	<0.001
Dyslipidemia	44.46%	40.40%	<0.001	1.06%	27.73%	<0.001	20.54%	17.71%	<0.001
CAD				56.98%	41.27%	<0.001	27.29%	17.78%	<0.001
CHF	21.15%	29.03%	<0.001				20.44%	21.36%	0.20
CKD	9.49%	9.24%	0.60	27.93%	21.62%	<0.001	15.28%	10.71%	<0.001
COPD	11.02%	10.84%	0.73	23.50%	16.67%	<0.001	28.19%	22.8%	<0.001
Diabetes	26.18%	29.62%	<0.001	33.75%	32.31%	0.09	22.78%	19.31%	<0.001
Arrhythmia	25.62%	27.03%	0.06	60.93%	54.23%	<0.001	28.36%	24.80%	<0.001
Stroke	3.35%	4.49%	<0.001	2.84%	2.42%	0.15	2.52%	1.67%	0.001
Length of stay									
Mean (SD)	5.42 (5.83)	5.67 (5.76)	0.01	6.02 (10.22)	5.71 (8.33)	0.07	5.36 (6.01)	5.13 (6.41)	0.04

AA: African American, ADHF: acute decompensated heart failure, AMI: acute myocardial infarction, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: chronic kidney disease, COPD: Chronic Obstructive Pulmonary Disease, NA: Native American, SD: standard deviation.

Table 2: Adjusted outcomes

	AMI		ADHF		Pneumonia	
Men vs. Women	Effect size (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
30 day mortality	OR: 0.98 (0.86, 1.11)	0.71	OR: 0.94 (0.82, 1.07)	0.39	OR: 1.19 (1.06, 1.34)	0.004
30 day readmission	OR: 0.90 (0.79, 1.04)	0.16	OR: 0.90 (0.82, 0.99)	0.03	OR: 1.10 (0.99, 1.23)	0.08

ADHF: acute decompensated heart failure, AMI: acute myocardial infarction, LOS: length of stay, OR: odds ratio.



Adjusted outcomes 30 day mortality and 30 day readmission in med vs. women

633x396mm (96 x 96 DPI)

Supplementary Table 1: ICD9 codes used in ADHF:

ICD-9	Frequency	%
428	8,665	70.65
428.1	97	0.79
428.2	7	0.06
428.21	305	2.49
428.22	99	0.81
428.23	1,021	8.32
428.3	24	0.2
428.31	243	1.98
428.32	80	0.65
428.33	787	6.42
428.4	6	0.05
428.41	109	0.89
428.42	50	0.41
428.43	742	6.05
428.9	30	0.24
Total	12,265	100

Supplementary Table 2: ICD9 codes used in AMI.

ICD-9	Frequency	%
410	3	0.02
410.01	536	3.4
410.02	2	0.01
410.1	34	0.22
410.11	2,186	13.86
410.12	11	0.07
410.2	5	0.03
410.21	466	2.95
410.22	3	0.02
410.3	4	0.03
410.31	309	1.96
410.32	2	0.01
410.4	9	0.06
410.41	2,688	17.04
410.42	17	0.11
410.5	4	0.03
410.51	256	1.62
410.52	2	0.01
410.6	1	0.01
410.61	75	0.48
410.7	25	0.16
410.71	8,345	52.89
410.72	58	0.37
410.8	6	0.04
410.81	331	2.1
410.82	2	0.01
410.9	7	0.04
410.91	389	2.47
410.92	1	0.01
Total	15,777	100

Supplementary Table 3: ICD9 codes used in pneumonia:

ICD-9	Frequency	%
11.6	1	0.01
11.64	1	0.01
52.1	10	0.08
73	2	0.02
115.05	68	0.53
115.95	29	0.22
480	1	0.01
480.1	67	0.52
480.2	1	0.01
480.3	1	0.01
480.8	12	0.09
480.9	57	0.44
481	431	3.33
482	68	0.53
482.1	208	1.61
482.2	163	1.26
482.3	57	0.44
482.31	11	0.09
482.32	6	0.05
482.39	15	0.12
482.4	66	0.51
482.41	140	1.08
482.42	57	0.44
482.49	2	0.02
482.81	8	0.06
482.82	33	0.26
482.83	118	0.91
482.84	46	0.36
482.89	42	0.32
482.9	143	1.11
483	25	0.19
483.8	5	0.04
484.1	3	0.02
484.6	1	0.01
485	104	0.8
486	8,520	65.9
487	234	1.81
495.8	4	0.03
495.9	62	0.48
506	12	0.09
507	2,081	16.1
507.1	6	0.05
507.8	2	0.02
997.32	6	0.05
Total	12,929	100

Supplementary Table 4: Comorbidities specified by OASH.

Dyslipidemia	Coronary Artery Disease	Depression	COPD
Arthritis	Substance abuse	Diabetes	Dementia
Osteoporosis	Congestive Heart Failure	Cancer	Schizophrenia
Autism	Chronic Kidney Disease	Arrhythmia	Hepatitis
Hypertension	Stroke	Asthma	HIV

Supplementary Table 5: List of ICD-9 codes used for the comorbidities:

The condition	ICD-9 codes used:
Dyslipidemia	272.0, 272.1, 272.2, 272.3, 272.4
Arthritis	714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91
Osteoporosis	733.00, 733.01, 733.02, 733.03, 733.09
Hypertension	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 362.11, 437.2
Coronary Artery Disease	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.8, 414.9
COPD	490, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496
Chronic Kidney Disease	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Stroke	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01,434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Depression	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 2 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03,

	250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 366.41
Cancer	Female breast cancer: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3. Colorectal cancer: 154.0, 154.1, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 230.3, 230.4, V10.05. Prostate cancer: 185, 233.4, V10.46. Lung cancer: 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11.
Arrhythmia	427.31
Asthma	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Dementia	331.0, 331.1, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.8, 797

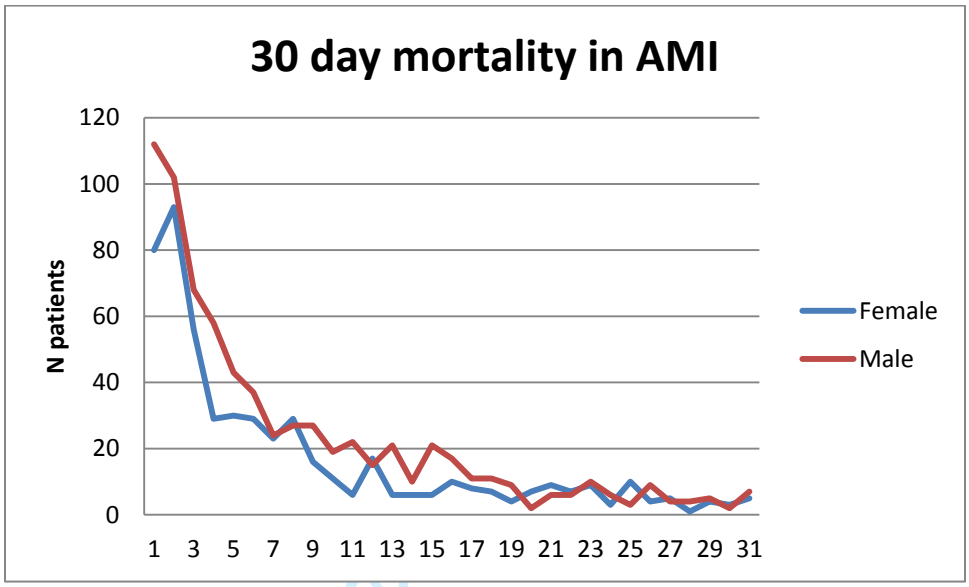
Supplementary Table 6: sensitivity analysis for the last 5 years of the study

Last 5 years	AMI	ADHF	Pneumonia
Men vs. Women	OR (95% CI)	OR (95% CI)	OR (95% CI)
30 day mortality	1.02 (0.73 to 1.43)	0.81 (0.62 to 1.06)	1.12 (0.85 to 1.47)
30 day readmission	0.85 (0.63 to 1.15)	0.78 (0.63 to 0.97)	0.94 (0.74 to 1.20)

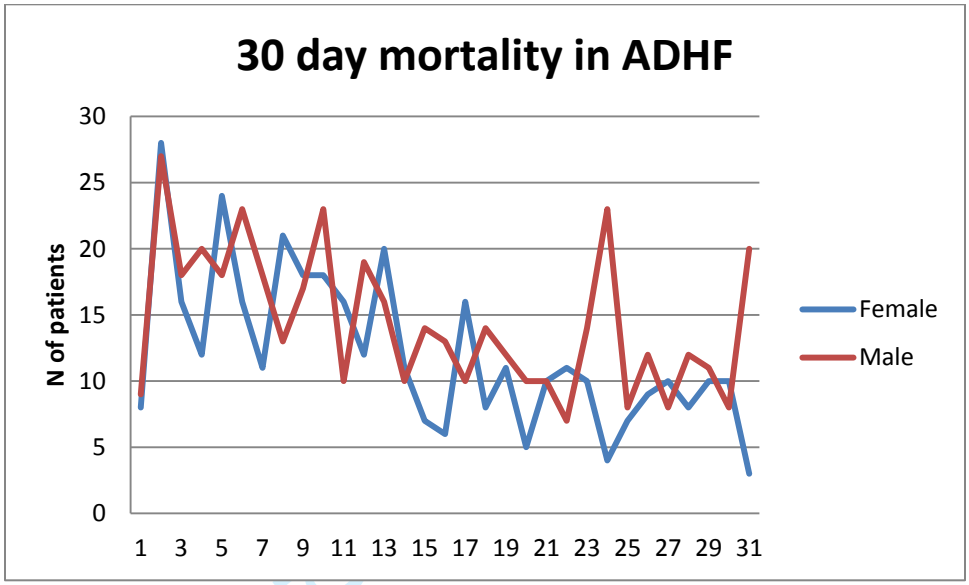
Supplementary Table 7: sensitivity analysis for 15 day mortality and readmission

Last 5 years	AMI	ADHF	Pneumonia
Men vs. Women	OR (95% CI)	OR (95% CI)	OR (95% CI)
15 day mortality	1.00 (0.88 to 1.15)	0.88 (0.73 to 1.05)	1.15 (1.00 to 1.33)
15 day readmission	0.91 (0.81 to 1.03)	0.93 (0.81 to 1.06)	1.10 (0.96 to 1.27)

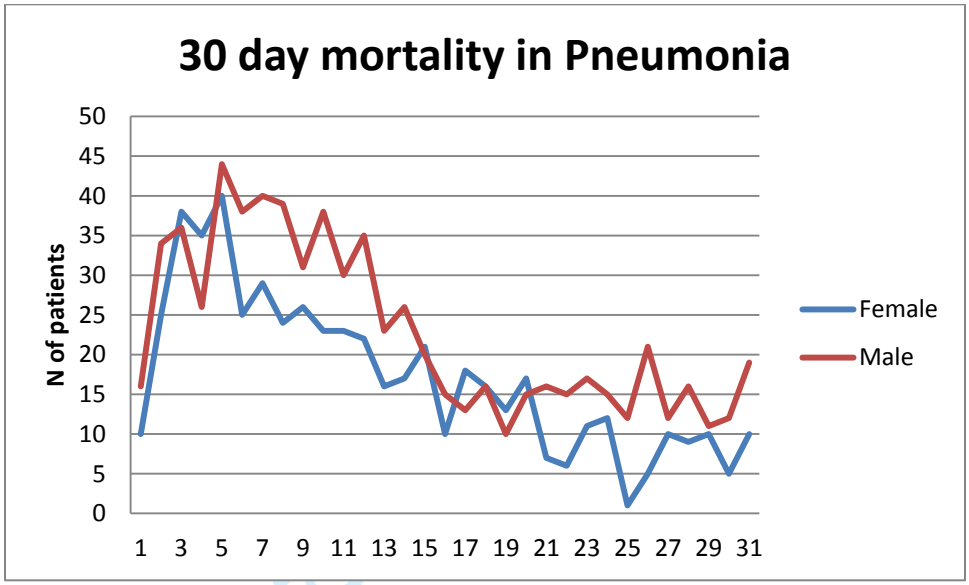
Supplementary Figure 1: 30 day mortality in AMI



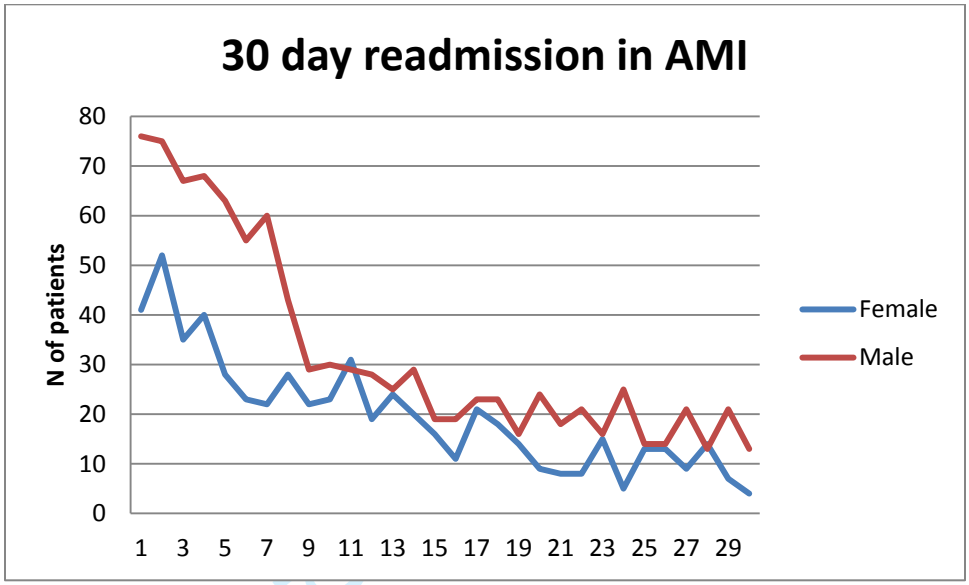
Supplementary Figure 2: 30 day mortality in ADHF



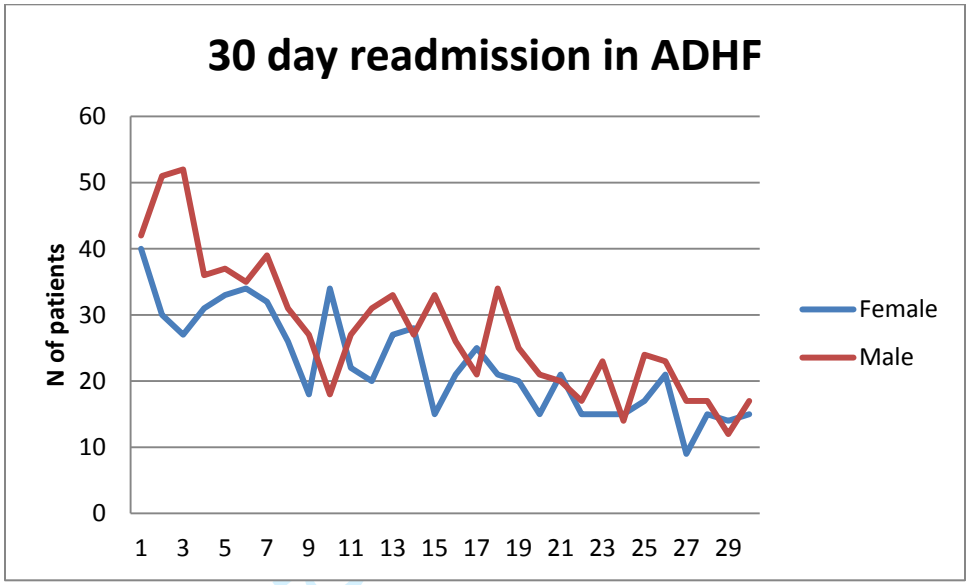
Supplementary Figure 3: 30 day mortality in pneumonia



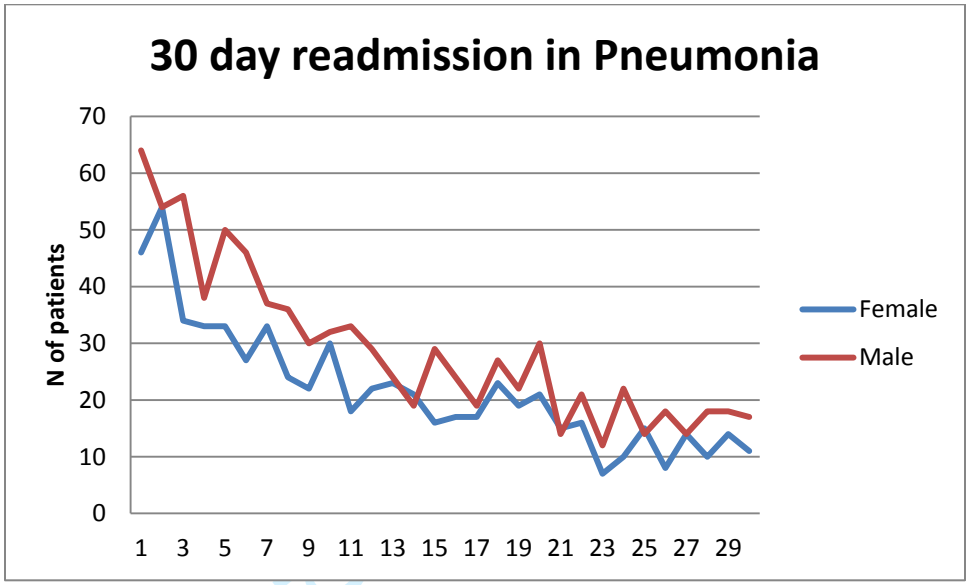
Supplementary Figure 4: 30 day readmission in AMI



Supplementary Figure 5: 30 day readmission in ADHF



Supplementary Figure 6: 30 day readmission in pneumonia



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**Page number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*9-11*
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Gender Disparities among Hospitalized Patients, a retrospective cohort study

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Gender Disparities among Hospitalized Patients, a retrospective cohort study

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Abstract:

Objective: To assess gender disparity in outcomes among hospitalized patients with acute myocardial infarction (AMI), acute decompensated heart failure (ADHF), or pneumonia.

Design: A retrospective cohort study.

Setting: A tertiary referral center in Midwest, USA.

Participants: We evaluated 12,265 adult patients hospitalized with ADHF, 15,777 with AMI and 12,929 with pneumonia, from January 1, 1995 through August 31, 2015. Patients were selected using ICD-9 codes.

Primary and secondary outcome measures: Prevalence of comorbidities, 30 day mortality, and 30 day readmission. Comorbidities were chosen from the twenty chronic conditions, specified by the Office of the Assistant Secretary for Health. Logistic regression analysis was conducted adjusting for multiple confounders.

Results: Prevalence of comorbidities was significantly different between men and women in all 3 conditions. After adjusting for age, length of stay, multi-comorbidities, and residence, there was no significant difference in 30 day mortality between men and women in AMI or ADHF, but men with pneumonia had slightly higher 30 day mortality with an odds ratio (OR) of 1.19 (95% CI 1.06 to 1.34). There was no significant difference in 30 day readmission between men and women with AMI or pneumonia, but women with ADHF were slightly more likely to be readmitted within 30 days with OR 0.90 (95% CI 0.82 to 0.99).

Conclusion: Gender differences in the distribution of comorbidities exist in patients hospitalized with AMI, ADHF, and pneumonia. However, there is minimal clinically

meaningful impact of these differences on outcomes. Efforts to address gender difference may need to be diverted towards targeting overall population health, reducing race/ethnicity disparity, and improving access to care.

Article summary:

Strengths and limitations of this study:

- The strengths of this study include the large sample size, multivariable adjustment and sensitivity analyses to assess robustness of findings.
- A limitation of this study is including all patients that were hospitalized in a single regional tertiary center; these patients were from several different states and some from were from other countries. We might have under estimated the mortality or readmission rates if these patients were readmitted to a different hospital closer to their residency place after discharge.
- A limitation of this study is that the majority of the included patients were white; the results may not be generalizable to people from other races.

Introduction:

Acute decompensated heart failure (ADHF), acute myocardial infarction (AMI), and pneumonia are among the most common causes of hospitalization in the United States, with more than 2.5 million hospitalizations per year, and estimated annual hospital cost of $31.3 billion.[1,2] Hospitalized patients with ADHF, AMI, or pneumonia are at high risk of death and readmission at 30 days after index hospitalization.[1,2] In the United States, 15.1% of patients with acute myocardial infarction (AMI), 11.4% of patients with ADHF, and 11.3% patients with pneumonia die within 30 days after hospitalization for respective disorders.[3,4] Likewise, 24.8%, 19.9% and 18.3% of patients hospitalized for ADHF, AMI, and pneumonia respectively are readmitted within 30 days of the first hospitalization.[5] Annually, the Centers for Medicare & Medicaid Services (CMS) publically reports a comprehensive overview of national performance as part of the Hospital Inpatient Quality Reporting (IQR) Program, using these three conditions. [1,2] Risk standardized 30-day mortality and readmission rates are quality performance measures for AMI, ADHF, and pneumonia.[6] However, these outcomes vary between males and females.[5]

In the past several decades, gender disparities in clinical outcomes of hospitalized patients with different diseases have been investigated.[7,8] Several studies suggested gender differences in clinical outcomes for patients with AMI, ADHF and Pneumonia.[9-12] Females have worse outcomes for pneumonia than males, with adjusted risk ratio of 1.15 for 28 days mortality.[13] Women with acute coronary syndromes were at a higher risk for unadjusted in-hospital death (5.6% vs. 4.3%)[8] and they are more likely to have adverse outcomes (myocardial infarction, stroke and readmission) compared to men (odds ratio 1.24, 95% CI 1.14 to 1.34).[14]

Although no gender differences were found in outcomes in patients with ADHF, there were significant gender differences in the clinical characteristics at presentation including age and comorbidities.[9]

Multimorbidity, defined as existence of two or more disorders in an individual patient, has become a public health issue of increasing magnitude. Around one third of all Americans have multimorbidity (31.5%), and the rate is expected to increase with time.[15] Multimorbidity is associated with premature death, propensity for over investigation, duplicate tests, medication non-adherence, polypharmacy with increased risk for drug adverse events, and a decline in functional status.[15] Mutlimorbidity itself may have gender disparities. The US National Health and Nutrition Examination Survey (NHANES) when looking at persons 65 years and older found that 83% of women compared to 65% men with coronary artery disease had one of the four comorbid conditions (arthritis, chronic lower respiratory tract disease , diabetes mellitus, and stroke).[16] European data suggest a similar difference in prevalence of multimorbidity between men and women.[17]

Although the above data provide sex-related differences in the prevalence of multimorbidity in specific patient population, the disparity in rates of occurrence of comorbid conditions and their impact on early clinical outcome have not been reported by gender for broader hospitalized patients with ADHF, AMI, and pneumonia.

To address this gap in knowledge, we evaluated gender-specific differences in prevalence of individual and multiple comorbid conditions in a large hospital-based patient population with ADHF, AMI, and pneumonia. Furthermore, we determined whether the

presence of individual or multimorbidity impacts 30-day mortality or readmission by gender independent of demographic and social characteristics.

Methods:

Study design and Population sample:

This is a retrospective study of patients aged ≥18 years hospitalized for ADHF, AMI, and pneumonia at Mayo Clinic, Rochester, Minnesota, from January 1, 1995 to August 31, 2015.

We included first hospitalization in the analysis when a patient had multiple repeat hospitalizations for the same condition, since patients with multiple hospitalizations with the same condition may have higher risk of readmission or mortality within 30 days. The data were extracted by dedicated abstraction personnel using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (supplementary tables 1-3). We abstracted data-related to age, gender, race, zip code, insurance, principal discharge diagnosis, secondary diagnoses, length of hospital stay, death, and readmission by date. The diagnoses of AMI, ADHF, and pneumonia were based on physician provider as documented in clinical notes. Patients who refused participation in clinical research were excluded. The study was approved by the Mayo Clinic Institutional Review Board.

Patient and Public Involvement: patients and public were not involved.

Measure of multi-comorbidities:

Comorbidities were chosen from twenty chronic conditions (Supplementary Table 4) specified by the Office of the Assistant Secretary for Health (OASH) [18] using ICD-9-CM codes (Supplementary table 5). Multi-comorbidities were categorized into four groups based on the number of existing chronic conditions: less than 2 comorbidities, 2 comorbidities, 3 comorbidities, and 4 or more comorbidities.

We did not use composite morbidity index such as Charlson, since it needed to be modified for this study. For example, we did not count coronary artery disease (CAD) as one of the comorbidities for patients hospitalized for AMI, the same for congestive heart failure for patients with ADHF.

We excluded 4-comorbid conditions (autism, schizophrenia, hepatitis, and HIV) from the analysis because of very low frequency of occurrence (<1%)..

Measures of outcomes:

The primary outcomes were prevalence of comorbidities in men and women, 30 day mortality, defined as 30 days from the day of admission with one of the primary diagnosis, and 30 day readmission for any cause since discharge date.

Statistical analysis:

Baseline characteristic data were summarized as mean and standard deviation for continuous variables and as for categorical variables. Prevalence of comorbidities and the number of multi-morbidities in men and women were compared using Chi^2 tests. Gender differences in 30 day mortality and 30 day readmission were presented as odds ratio. Logistic regression models were developed to estimate the risk of outcomes of interest while controlling for various confounders (age, length of stay, Olmsted county residency, and number of comorbidities). Results are reported as odds ratios and 95% confidence intervals (CI). A two-tailed P value <0.05 was considered as statistically significant and all analyses were performed using STATA 14.0 (StataCorp, College Station, Texas).

Results:

40,971 patients were included during the study period, 12,265 with ADHF, 15,777 with AMI, and 12,929 with pneumonia. There were more men in all three conditions, and men were younger. (Table 1)

The prevalence of each comorbidity in men and women were reported in Table 1. The majority of deaths due to AMI occurred in the first 10 days; whereas this trend was not evidence for pneumonia or ADHF (Supplementary figures 1-3). The majority of readmissions for all three conditions occurred in the first 15 days (Supplementary figures 4-6).

Summary of outcomes

ADHF:

12,265 patients were hospitalized with ADHF within the study period, 7,010 men and 5,255 women. Women were older with a mean age of 75.4 years compared to 72.3 years in men. 85.75% of both men and women were Caucasian. 71.94 % of men had multi-comorbidities compared to 69.99 % of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 0.94 (95% CI: 0.82, 1.07), OR for 30 day readmission 0.90 (95% CI: 0.82, 0.99). (Table 2), (Figure 1)

A subgroup analysis including patients who had CAD was conducted, OR for 30 day mortality was 0.89 (0.73 to 1.09) p=0.27, and OR for 30 day readmission was 0.90 (0.75 to 1.082) p=0.27.

AMI:

Of the 15,777 patients hospitalized with AMI 10,280 were men and 5,497 were women. Women were older, with a mean age of 73 years compared to 66.5 years in men. 86.78% of patients were Caucasian (87% of men and 86% in women) (Table 1). 46.73 % of men had multi-comorbidities compared to 52.17 % of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 0.98 (95% CI: 0.86, 1.11), OR for 30 day readmission 0.90 (95% CI: 0.79, 1.04). (Table 2) (Figure 1)

A subgroup analysis including patients who had heart failure was conducted, OR for 30 day mortality was 1.18 (1.007 to 1.37) p=0.04, and OR for 30 day readmission: 0.89 (0.72 to 1.09) p=0.26.

Pneumonia:

Of the 12,929 patients hospitalized with pneumonia within the study period, three were 7,073 men and 5,856 women. Women were older with a mean age of 70.8 compared to 69.2 years in men. 85% of both men and women were Caucasian. 58.89% of men had multi-comorbidities compared to 55.79% of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 1.19 (95% CI 1.06, 1.34), OR for 30 day readmission 1.10 (95% CI 0.99, 1.23). (Table 2) (Figure 1)

A subgroup analysis including patients who had CAD was conducted, OR for 30 day mortality was 1.21 (0.93 to 1.56) p=0.15, and OR for 30 day readmission was 1.06 (0.81 to 1.39) p=0.65.

A subgroup analysis including patients who had heart failure was conducted, OR for 30 day mortality was 30 day mortality was 1.089 (0.89 to 1.33) p=0.404, and OR for 30 day readmission: 1.21 (1.007 to 1.46) p=0.042.

Sensitivity analysis:

To determine the contemporary status of gender disparities and comorbidities, we conducted a sensitivity analysis focusing on patients who were admitted in the last 5 years. The results were overall consistent with the main analysis, except for 30 day mortality for pneumonia (which became nonsignificant between men and women whereas mortality was marginally higher in men, in the original analysis). (Supplementary table 6).

We conducted another sensitivity analysis, looking for 15 day mortality and readmission. There were no statistically significant differences in 15 day readmission between men and women in all 3 conditions. 15 day mortality was marginally higher for pneumonia in men OR: 1.15 (95% CI: 1.00 to 1.33) but not statistically significant different in AMI or ADHF (Supplementary table 7).

Discussion:

This study suggests that comorbidities are distributed differently between men and women hospitalized for ADHF, AMI and pneumonia. Despite a fairly large sample size, this study showed that gender differences appear to have minimal meaningful impact on outcomes.

In AMI, women are known to less commonly report chest pain or discomfort compared with men, this may lead to gender differences in outcomes of AMI.[19] However, in our study, the gender difference in 30-day mortality could be explained by the age difference,

women were 6.5 years older in average. After adjusting for residency location and number of comorbidities, age had a significant impact on 30 day mortality, but not gender or multi-comorbidities. On the other hand, the only factor that had a significant association with 30 day readmission was multi-comorbidities.

In ADHF, men had significantly lower 30 day readmission rate compared to women, while they did not have a significant difference in 30 day mortality. A sensitivity analysis including only patients for the last 5 years, showed similar results. Multi-comorbidity did not have a significant effect on 30 day mortality or readmission. This might be explained by difference in symptoms presentations, or difference in access to medical care between men and women. For example, men used to have higher invasive cardiac procedures than women in a previously published study.[20]

Men with pneumonia had significantly higher 30 day mortality compared to women, but no significant difference in 30 day readmission. Multi- comorbidities had a significant effect on 30 day readmission in men but not in women.

Comparison with existing literature

Our findings in AMI were consistent with previously published studies[11,21] that showed a higher 30 day mortality rate in women verses men, but no significant difference after adjustment for other variables. In these studies, they include elderly patients only (> 65 years old) while we had no age restriction, but yet, in all of these studies, women were older, and had differences in comorbidities compared to men. In ADHF, our results were consistent with a previously published study that used ADHERE (Acute Decompensated Heart Failure National Registry) between 2001 and 2004[9], in both studies there was no significant difference in in-hospital mortality between men and women.

In pneumonia, our study showed that men have worse outcomes than women, unlike a previous study[13] that found that women have worse outcomes for community-acquired pneumonia with 28-day mortality odds ratio of 1.15 (95% CI 1.02–1.30). Howver, our study included all types of pneumonia, and it was consistent with another study that used the Medicare database and showed worse outcomes in men[22].

Limitations and strengths

A limitation of this study is that we used ICD-9 codes for identifying patients. It was not feasible to review charts for such a large number of patients; and therefore, we had to depend on administrative and billing codes. New research using the recent ICD-10 coding is needed to study the consistency of prevalence and implication of comorbidities on early outcomes in hospitalized patients. Another limitation is that we included all patients that were hospitalized in a single regional tertiary center; these patients were from several different states and some from were from other countries. We might have under estimated the mortality or readmission rates if these patients were readmitted to a different hospital closer to their residency place after discharge. Making this less concerning is the fact that we found, gender to be an independent variable from residency place; in addition, we adjusted for residency place (Olmsted County where the hospital is vs. non Olmsted County). Another limitation is that the majority of our included patients were white; our results may not be generalizable to people from other races. Other limitation in our data is that we have included only the first hospitalization; some patients have likely had multiple repeat hospitalizations for the same condition. The strengths of this study include the large sample size, multivariable adjustment and sensitivity analyses to assess robustness of findings.

Clinical and policy implication:

Although this study showed that women hospitalized for ADHF had higher 30 day readmission rate, the absolute risk was small with a number needed to harm of 88 patients (95% CI: 48, 445). For pneumonia, women had lower mortality, with a number needed to harm of 61 patients (95% CI: 36, 202). With this minimal clinically meaningful impact of these differences on the early outcomes of these three important conditions; efforts to address gender difference may need to be diverted towards targeting overall population health, where outcomes of these conditions are still suboptimal in both genders, or towards reducing race/ethnicity disparity, or improving access to care differences.

Conclusion:

Gender disparities interact with comorbidities and impact mortality and readmission. However, this effect varies according to the conditions, seems to be unpredictable and has a minimal meaningful impact on outcomes.

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Legends:

Table 1: Baseline characteristics

Table 2: Adjusted outcomes

Figure 1: Adjusted outcomes 30 day mortality and 30 day readmission in men vs. women.

Table 1: Baseline characteristics

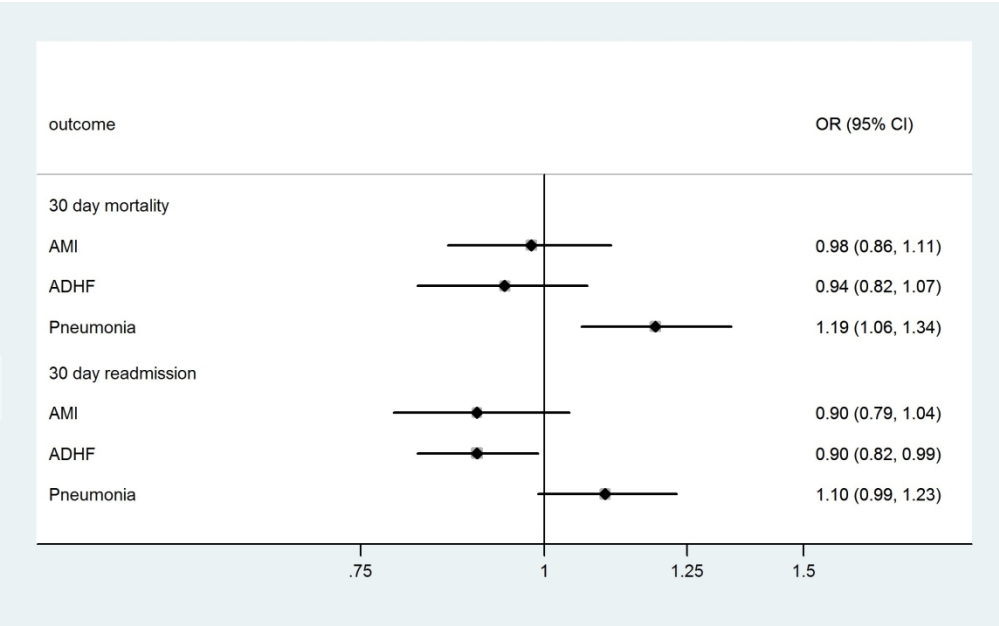
	AMI = 15,777			ADHF =12,265			Pneumonia = 12,929		
	Men 65%	Women 35%	P value	Men 57%	Women 43%	P value	Men 55%	Women 45%	P value
Age (SD)	66.5 (13.3)	73 (13.3)	<0.001	72.3 (13)	75.4 (13.9)	<0.001	69.2 (16.8)	70.8 (17.7)	<0.001
Race %									
Non-white	12.74%	14.12%	0.015	14.25%	14.25%	0.997	15.65%	14.70%	0.14
White	87.26%	85.88%		85.75%	85.75%		84.35%	85.30%	
Comorbidity									
Arthritis	3.37%	5.57%	0.06	4.35%	6.95%	<0.001	4.28%	7.26%	<0.001
Asthma	2.42%	3.89%	<0.001	2.81%	5.25%	<0.001	5.09%	10.31%	<0.001
Dementia	1.73%	3.29%	<0.001	2.65%	4.17%	<0.001	6.9%	8.52%	0.001
Depression	4.4%	6.8%	<0.001	6.28%	9.12%	<0.001	8.64%	12.93%	<0.001
Hypertension	57.64%	65.69%	<0.001	56.52%	62.11%	<0.001	43.91%	48.80%	<0.001
Osteoporosis	0.4%	4.73%	<0.001	0.97%	7.16%	<0.001	2.09%	9.00%	<0.001
Cancer	8.14%	6.95%	0.01	13.42%	11.91%	0.01	25.93%	17.81%	<0.001
Drug abuse	4.15%	1.47%	<0.001	3.65%	0.97%	<0.001	4.54%	2.36%	<0.001
Dyslipidemia	44.46%	40.40%	<0.001	1.06%	27.73%	<0.001	20.54%	17.71%	<0.001
CAD				56.98%	41.27%	<0.001	27.29%	17.78%	<0.001
CHF	21.15%	29.03%	<0.001				20.44%	21.36%	0.20
CKD	9.49%	9.24%	0.60	27.93%	21.62%	<0.001	15.28%	10.71%	<0.001
COPD	11.02%	10.84%	0.73	23.50%	16.67%	<0.001	28.19%	22.8%	<0.001
Diabetes	26.18%	29.62%	<0.001	33.75%	32.31%	0.09	22.78%	19.31%	<0.001
Arrhythmia	25.62%	27.03%	0.06	60.93%	54.23%	<0.001	28.36%	24.80%	<0.001
Stroke	3.35%	4.49%	<0.001	2.84%	2.42%	0.15	2.52%	1.67%	0.001
Length of stay									
Mean (SD)	5.42 (5.83)	5.67 (5.76)	0.01	6.02 (10.22)	5.71 (8.33)	0.07	5.36 (6.01)	5.13 (6.41)	0.04

AA: African American, ADHF: acute decompensated heart failure, AMI: acute myocardial infarction, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: chronic kidney disease, COPD: Chronic Obstructive Pulmonary Disease, NA: Native American, SD: standard deviation.

Table 2: Adjusted outcomes

	AMI		ADHF		Pneumonia	
Men vs. Women	Effect size (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
30 day mortality	OR: 0.98 (0.86, 1.11)	0.71	OR: 0.94 (0.82, 1.07)	0.39	OR: 1.19 (1.06, 1.34)	0.004
30 day readmission	OR: 0.90 (0.79, 1.04)	0.16	OR: 0.90 (0.82, 0.99)	0.03	OR: 1.10 (0.99, 1.23)	0.08

ADHF: acute decompensated heart failure, AMI: acute myocardial infarction, LOS: length of stay, OR: odds ratio.



Adjusted outcomes 30 day mortality and 30 day readmission in med vs. women

633x396mm (96 x 96 DPI)

Supplementary Table 1: ICD9 codes used in ADHF:

ICD-9	Frequency	%
428	8,665	70.65
428.1	97	0.79
428.2	7	0.06
428.21	305	2.49
428.22	99	0.81
428.23	1,021	8.32
428.3	24	0.2
428.31	243	1.98
428.32	80	0.65
428.33	787	6.42
428.4	6	0.05
428.41	109	0.89
428.42	50	0.41
428.43	742	6.05
428.9	30	0.24
Total	12,265	100

Frequency: Number of patients that were diagnosed based on that code.
%: The percentage of the code out of total number of patients

Supplementary Table 2: ICD9 codes used in AMI.

ICD-9	Frequency	%
410	3	0.02
410.01	536	3.4
410.02	2	0.01
410.1	34	0.22
410.11	2,186	13.86
410.12	11	0.07
410.2	5	0.03
410.21	466	2.95
410.22	3	0.02
410.3	4	0.03
410.31	309	1.96
410.32	2	0.01
410.4	9	0.06
410.41	2,688	17.04
410.42	17	0.11
410.5	4	0.03
410.51	256	1.62
410.52	2	0.01
410.6	1	0.01
410.61	75	0.48
410.7	25	0.16
410.71	8,345	52.89
410.72	58	0.37
410.8	6	0.04
410.81	331	2.1
410.82	2	0.01
410.9	7	0.04
410.91	389	2.47
410.92	1	0.01
Total	15,777	100

Frequency: Number of patients that were diagnosed based on that code.
%: The percentage of the code out of total number of patients

Supplementary Table 3: ICD9 codes used in pneumonia:

ICD-9	Frequency	%
11.6	1	0.01
11.64	1	0.01
52.1	10	0.08
73	2	0.02
115.05	68	0.53
115.95	29	0.22
480	1	0.01
480.1	67	0.52
480.2	1	0.01
480.3	1	0.01
480.8	12	0.09
480.9	57	0.44
481	431	3.33
482	68	0.53
482.1	208	1.61
482.2	163	1.26
482.3	57	0.44
482.31	11	0.09
482.32	6	0.05
482.39	15	0.12
482.4	66	0.51
482.41	140	1.08
482.42	57	0.44
482.49	2	0.02
482.81	8	0.06
482.82	33	0.26
482.83	118	0.91
482.84	46	0.36
482.89	42	0.32
482.9	143	1.11
483	25	0.19
483.8	5	0.04
484.1	3	0.02
484.6	1	0.01
485	104	0.8
486	8,520	65.9
487	234	1.81
495.8	4	0.03
495.9	62	0.48
506	12	0.09
507	2,081	16.1
507.1	6	0.05
507.8	2	0.02
997.32	6	0.05
Total	12,929	100

Frequency: Number of patients that were diagnosed based on that code.
%: The percentage of the code out of total number of patients

Supplementary Table 4: Comorbidities specified by OASH.

Dyslipidemia	Coronary Artery Disease	Depression	COPD
Arthritis	Substance abuse	Diabetes	Dementia
Osteoporosis	Congestive Heart Failure	Cancer	Schizophrenia
Autism	Chronic Kidney Disease	Arrhythmia	Hepatitis
Hypertension	Stroke	Asthma	HIV

Supplementary Table 5: List of ICD-9 codes used for the comorbidities:

The condition	ICD-9 codes used:
Dyslipidemia	272.0, 272.1, 272.2, 272.3, 272.4
Arthritis	714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91
Osteoporosis	733.00, 733.01, 733.02, 733.03, 733.09
Hypertension	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 362.11, 437.2
Coronary Artery Disease	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.8, 414.9
COPD	490, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496
Chronic Kidney Disease	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Stroke	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01,434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Depression	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 2 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03,

	250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 366.41
Cancer	Female breast cancer: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3. Colorectal cancer: 154.0, 154.1, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 230.3, 230.4, V10.05. Prostate cancer: 185, 233.4, V10.46. Lung cancer: 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11.
Arrhythmia	427.31
Asthma	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Dementia	331.0, 331.1, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.8, 797

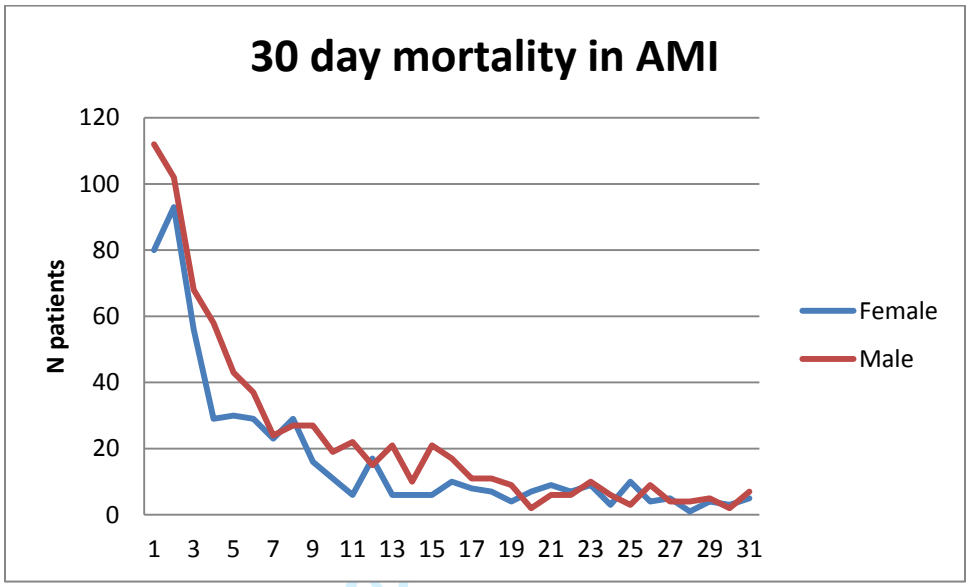
Supplementary Table 6: sensitivity analysis for the last 5 years of the study

Last 5 years	AMI	ADHF	Pneumonia
Men vs. Women	OR (95% CI)	OR (95% CI)	OR (95% CI)
30 day mortality	1.02 (0.73 to 1.43)	0.81 (0.62 to 1.06)	1.12 (0.85 to 1.47)
30 day readmission	0.85 (0.63 to 1.15)	0.78 (0.63 to 0.97)	0.94 (0.74 to 1.20)

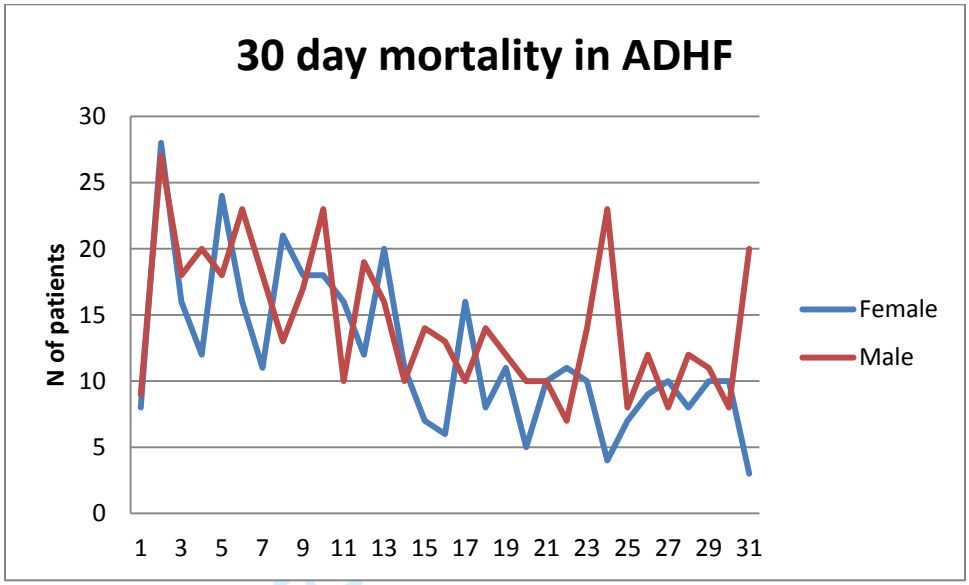
Supplementary Table 7: sensitivity analysis for 15 day mortality and readmission

Last 5 years	AMI	ADHF	Pneumonia
Men vs. Women	OR (95% CI)	OR (95% CI)	OR (95% CI)
15 day mortality	1.00 (0.88 to 1.15)	0.88 (0.73 to 1.05)	1.15 (1.00 to 1.33)
15 day readmission	0.91 (0.81 to 1.03)	0.93 (0.81 to 1.06)	1.10 (0.96 to 1.27)

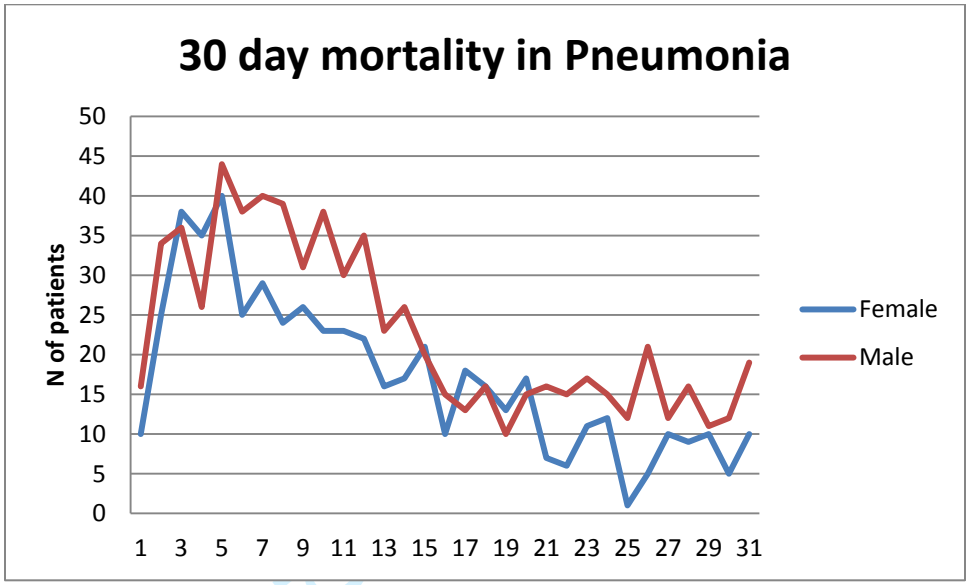
Supplementary Figure 1: 30 day mortality in AMI



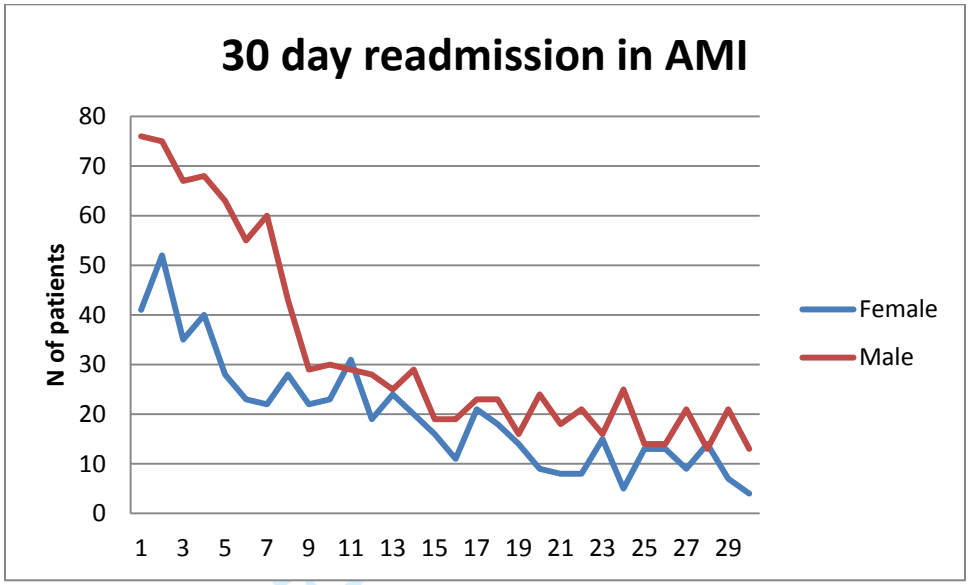
Supplementary Figure 2: 30 day mortality in ADHF



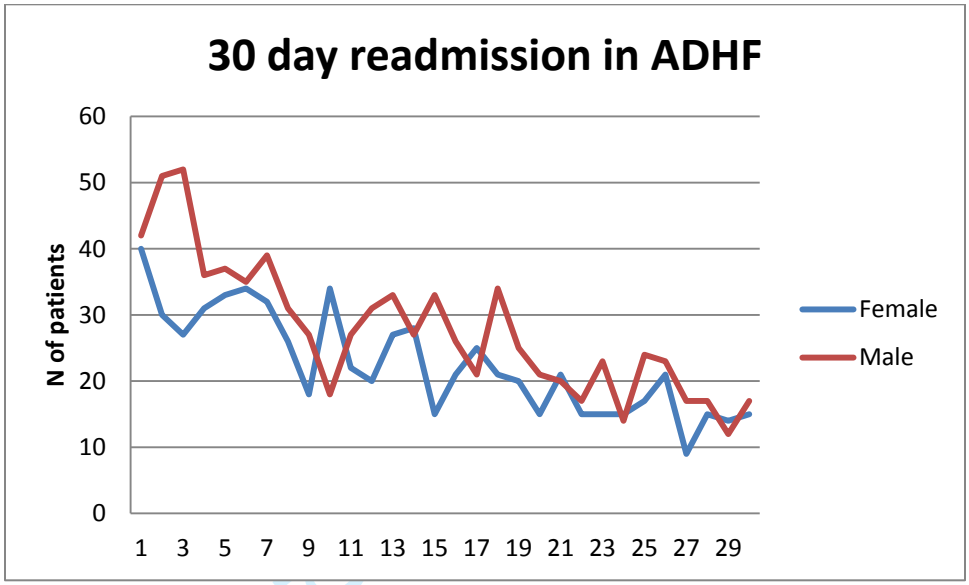
Supplementary Figure 3: 30 day mortality in pneumonia



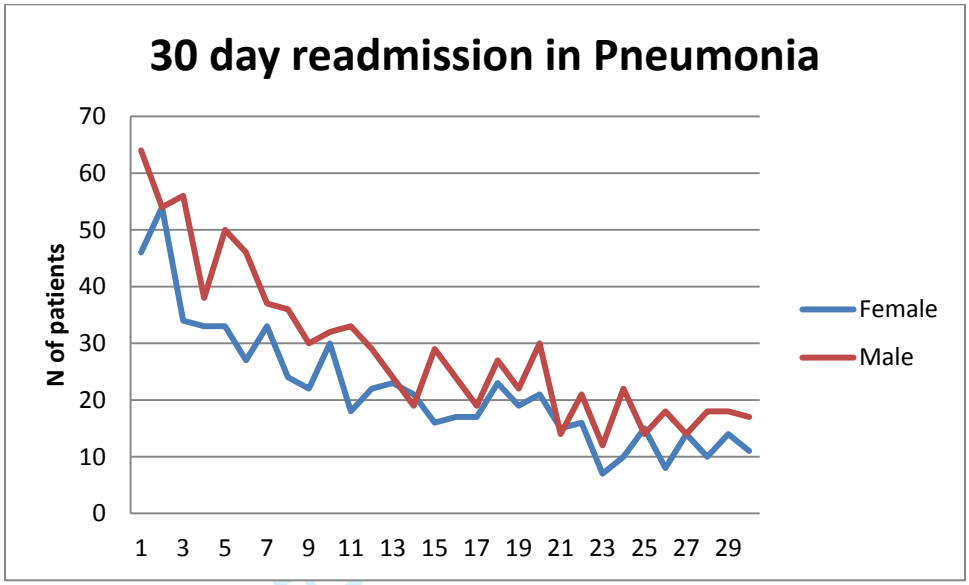
Supplementary Figure 4: 30 day readmission in AMI



Supplementary Figure 5: 30 day readmission in ADHF



Supplementary Figure 6: 30 day readmission in pneumonia



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			Page number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*9-11*
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Gender disparities among hospitalized patients with acute myocardial infarction, acute decompensated heart failure, or pneumonia: a retrospective cohort study

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Gender disparities among hospitalized patients with acute myocardial infarction, acute decompensated heart failure, or pneumonia: a retrospective cohort study

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Abstract:

Objective: To assess gender disparity in outcomes among hospitalized patients with acute myocardial infarction (AMI), acute decompensated heart failure (ADHF), or pneumonia.

Design: A retrospective cohort study.

Setting: A tertiary referral center in Midwest, USA.

Participants: We evaluated 12,265 adult patients hospitalized with ADHF, 15,777 with AMI and 12,929 with pneumonia, from January 1, 1995 through August 31, 2015. Patients were selected using ICD-9 codes.

Primary and secondary outcome measures: Prevalence of comorbidities, 30 day mortality, and 30 day readmission. Comorbidities were chosen from the twenty chronic conditions, specified by the Office of the Assistant Secretary for Health. Logistic regression analysis was conducted adjusting for multiple confounders.

Results: Prevalence of comorbidities was significantly different between men and women in all 3 conditions. After adjusting for age, length of stay, multi-comorbidities, and residence, there was no significant difference in 30 day mortality between men and women in AMI or ADHF, but men with pneumonia had slightly higher 30 day mortality with an odds ratio (OR) of 1.19 (95% CI 1.06 to 1.34). There was no significant difference in 30 day readmission between men and women with AMI or pneumonia, but women with ADHF were slightly more likely to be readmitted within 30 days with OR 0.90 (95% CI 0.82 to 0.99).

Conclusion: Gender differences in the distribution of comorbidities exist in patients hospitalized with AMI, ADHF, and pneumonia. However, there is minimal clinically

meaningful impact of these differences on outcomes. Efforts to address gender difference may need to be diverted towards targeting overall population health, reducing race/ethnicity disparity, and improving access to care.

Article summary:

Strengths and limitations of this study:

- The strengths of this study include the large sample size, multivariable adjustment and sensitivity analyses to assess robustness of findings.
- A limitation of this study is including all patients that were hospitalized in a single regional tertiary center; these patients were from several different states and some from were from other countries. We might have under estimated the mortality or readmission rates if these patients were readmitted to a different hospital closer to their residency place after discharge.
- A limitation of this study is that the majority of the included patients were white; the results may not be generalizable to people from other races.

Introduction:

Acute decompensated heart failure (ADHF), acute myocardial infarction (AMI), and pneumonia are among the most common causes of hospitalization in the United States, with more than 2.5 million hospitalizations per year, and estimated annual hospital cost of $31.3 billion.[1,2] Hospitalized patients with ADHF, AMI, or pneumonia are at high risk of death and readmission at 30 days after index hospitalization.[1,2] In the United States, 15.1% of patients with acute myocardial infarction (AMI), 11.4% of patients with ADHF, and 11.3% patients with pneumonia die within 30 days after hospitalization for respective disorders.[3,4] Likewise, 21.4%, 16% and 16.5% of patients hospitalized for ADHF, AMI, and pneumonia respectively are readmitted within 30 days of the first hospitalization.[5] Annually, the Centers for Medicare & Medicaid Services (CMS) publically reports a comprehensive overview of national performance as part of the Hospital Inpatient Quality Reporting (IQR) Program, using these three conditions. [1,2] Risk standardized 30-day mortality and readmission rates are quality performance measures for AMI, ADHF, and pneumonia.[6] However, these outcomes vary between males and females.[7]

In the past several decades, gender disparities in clinical outcomes of hospitalized patients with different diseases have been investigated.[8,9] Several studies suggested gender differences in clinical outcomes for patients with AMI, ADHF and Pneumonia.[10-13]

Females have worse outcomes for pneumonia than males, with adjusted risk ratio of 1.15 for 28 days mortality.[14] Women with acute coronary syndromes were at a higher risk for unadjusted in-hospital death (5.6% vs. 4.3%)[9] and they are more likely to have adverse

outcomes (myocardial infarction, stroke and readmission) compared to men (odds ratio 1.24, 95% CI 1.14 to 1.34).[15]

Although no gender differences were found in outcomes in patients with ADHF, there were significant gender differences in the clinical characteristics at presentation including age and comorbidities.[10]

Multimorbidity, defined as existence of two or more disorders in an individual patient, has become a public health issue of increasing magnitude. Around one third of all Americans have multimorbidity (31.5%), and the rate is expected to increase with time.[16] Multimorbidity is associated with premature death, propensity for over investigation, duplicate tests, medication non-adherence, polypharmacy with increased risk for drug adverse events, and a decline in functional status.[16] Mutlimorbidity itself may have gender disparities. The US National Health and Nutrition Examination Survey (NHANES) when looking at persons 65 years and older found that 83% of women compared to 65% men with coronary artery disease had one of the four comorbid conditions (arthritis, chronic lower respiratory tract disease , diabetes mellitus, and stroke).[17] European data suggest a similar difference in prevalence of multimorbidity between men and women.[18]

Although the above data provide sex-related differences in the prevalence of multimorbidity in specific patient population, the disparity in rates of occurrence of comorbid conditions and their impact on early clinical outcome have not been reported by gender for broader hospitalized patients with ADHF, AMI, and pneumonia.

To address this gap in knowledge, we evaluated gender-specific differences in prevalence of individual and multiple comorbid conditions in a large hospital-based patient

population with ADHF, AMI, and pneumonia. Furthermore, we determined whether the presence of individual or multimorbidity impacts 30-day mortality or readmission by gender independent of demographic and social characteristics.

Methods:

Study design and Population sample:

This is a retrospective study of patients aged ≥18 years hospitalized for ADHF, AMI, and pneumonia at Mayo Clinic, Rochester, Minnesota, from January 1, 1995 to August 31, 2015.

We included first hospitalization in the analysis when a patient had multiple repeat hospitalizations for the same condition, since patients with multiple hospitalizations with the same condition may have higher risk of readmission or mortality within 30 days. The data were extracted by dedicated abstraction personnel using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (supplementary tables 1-3). We abstracted data-related to age, gender, race, zip code, insurance, principal discharge diagnosis, secondary diagnoses, length of hospital stay, death, and readmission by date. The diagnoses of AMI, ADHF, and pneumonia were based on physician provider as documented in clinical notes. Patients who refused participation in clinical research were excluded. The study was approved by the Mayo Clinic Institutional Review Board.

Patient and Public Involvement: patients and public were not involved.

Measure of multi-comorbidities:

Comorbidities were chosen from twenty chronic conditions (Supplementary Table 4) specified by the Office of the Assistant Secretary for Health (OASH) [19] using ICD-9-CM codes (Supplementary table 5). Multi-comorbidities were categorized into four groups based on the number of existing chronic conditions: less than 2 comorbidities, 2 comorbidities, 3 comorbidities, and 4 or more comorbidities.

We did not use composite morbidity index such as Charlson, since it needed to be modified for this study. For example, we did not count coronary artery disease (CAD) as one of the comorbidities for patients hospitalized for AMI, the same for congestive heart failure for patients with ADHF.

We excluded 4-comorbid conditions (autism, schizophrenia, hepatitis, and HIV) from the analysis because of very low frequency of occurrence (<1%)..

Measures of outcomes:

The primary outcomes were prevalence of comorbidities in men and women, 30 day mortality, defined as 30 days from the day of admission with one of the primary diagnosis, and 30 day readmission for any cause since discharge date.

Statistical analysis:

Baseline characteristic data were summarized as mean and standard deviation for continuous variables and as for categorical variables. Prevalence of comorbidities and the number of multi-morbidities in men and women were compared using Chi^2 tests. Gender differences in 30 day mortality and 30 day readmission were presented as odds ratio. Logistic regression models were developed to estimate the risk of outcomes of interest while controlling for various confounders (age, length of stay, Olmsted county residency, and number of comorbidities). Results are reported as odds ratios and 95% confidence intervals (CI). A two-tailed P value <0.05 was considered as statistically significant and all analyses were performed using STATA 14.0 (StataCorp, College Station, Texas).

Results:

40,971 patients were included during the study period, 12,265 with ADHF, 15,777 with AMI, and 12,929 with pneumonia. There were more men in all three conditions, and men were younger. (Table 1)

The prevalence of each comorbidity in men and women were reported in Table 1. The majority of deaths due to AMI occurred in the first 10 days; whereas this trend was not evidence for pneumonia or ADHF (Supplementary figures 1-3). The majority of readmissions for all three conditions occurred in the first 15 days (Supplementary figures 4-6).

Summary of outcomes

ADHF:

12,265 patients were hospitalized with ADHF within the study period, 7,010 men and 5,255 women. Women were older with a mean age of 75.4 years compared to 72.3 years in men. 85.75% of both men and women were Caucasian. 71.94 % of men had multi-comorbidities compared to 69.99 % of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 0.94 (95% CI: 0.82 to 1.07), OR for 30 day readmission 0.90 (95% CI: 0.82 to 0.99). (Table 2), (Figure 1)

A subgroup analysis including patients who had CAD was conducted, OR for 30 day mortality was 0.89 (95% CI: 0.73 to 1.09), and OR for 30 day readmission was 0.90 (95% CI: 0.75 to 1.082).

AMI:

Of the 15,777 patients hospitalized with AMI 10,280 were men and 5,497 were women. Women were older, with a mean age of 73 years compared to 66.5 years in men. 86.78% of patients were Caucasian (87% of men and 86% in women) (Table 1). 46.73 % of men had multi-comorbidities compared to 52.17 % of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 0.98 (95% CI: 0.86 to 1.11), OR for 30 day readmission 0.90 (95% CI: 0.79 to 1.04). (Table 2) (Figure 1)

A subgroup analysis including patients who had heart failure was conducted, OR for 30 day mortality was 1.18 (95% CI: 1.007 to 1.37), and OR for 30 day readmission: 0.89 (95% CI: 0.72 to 1.09).

Pneumonia:

Of the 12,929 patients hospitalized with pneumonia within the study period, three were 7,073 men and 5,856 women. Women were older with a mean age of 70.8 compared to 69.2 years in men. 85% of both men and women were Caucasian. 58.89% of men had multi-comorbidities compared to 55.79% of women.

After adjusting for age, length of stay, residence place (Olmsted county vs. non-Olmsted), and multi-comorbidities, OR for 30 day mortality for men vs. women was 1.19 (95% CI 1.06 to 1.34), OR for 30 day readmission 1.10 (95% CI: 0.99 to 1.23). (Table 2) (Figure 1)

A subgroup analysis including patients who had CAD was conducted, OR for 30 day mortality was 1.21 (95% CI: 0.93 to 1.56), and OR for 30 day readmission was 1.06 (95% CI: 0.81 to 1.39).

A subgroup analysis including patients who had heart failure was conducted, OR for 30 day mortality was 30 day mortality was 1.089 (95% CI: 0.89 to 1.33), and OR for 30 day readmission: 1.21 (95% CI: 1.007 to 1.46).

Sensitivity analysis:

To determine the contemporary status of gender disparities and comorbidities, we conducted a sensitivity analysis focusing on patients who were admitted in the last 5 years. The results were overall consistent with the main analysis, except for 30 day mortality for pneumonia (which became nonsignificant between men and women whereas mortality was marginally higher in men, in the original analysis). (Supplementary table 6).

We conducted another sensitivity analysis, looking for 15 day mortality and readmission. There were no statistically significant differences in 15 day readmission between men and women in all 3 conditions. 15 day mortality was marginally higher for pneumonia in men OR: 1.15 (95% CI: 1.00 to 1.33) but not statistically significant different in AMI or ADHF (Supplementary table 7).

Discussion:

This study suggests that comorbidities are distributed differently between men and women hospitalized for ADHF, AMI and pneumonia. Despite a fairly large sample size, this study showed that gender differences appear to have minimal meaningful impact on outcomes.

In AMI, women are known to less commonly report chest pain or discomfort compared with men, this may lead to gender differences in outcomes of AMI.[20] However, in our study, the gender difference in 30-day mortality could be explained by the age difference,

women were 6.5 years older in average. After adjusting for residency location and number of comorbidities, age had a significant impact on 30 day mortality, but not gender or multi-comorbidities. On the other hand, the only factor that had a significant association with 30 day readmission was multi-comorbidities.

In ADHF, men had significantly lower 30 day readmission rate compared to women, while they did not have a significant difference in 30 day mortality. A sensitivity analysis including only patients for the last 5 years, showed similar results. Multi-comorbidity did not have a significant effect on 30 day mortality or readmission. This might be explained by difference in symptoms presentations, or difference in access to medical care between men and women. For example, men used to have higher invasive cardiac procedures than women in a previously published study.[21]

Men with pneumonia had significantly higher 30 day mortality compared to women, but no significant difference in 30 day readmission. Multi- comorbidities had a significant effect on 30 day readmission in men but not in women.

Comparison with existing literature

Our findings in AMI were consistent with previously published studies[12,22] that showed a higher 30 day mortality rate in women verses men, but no significant difference after adjustment for other variables. In these studies, they include elderly patients only (> 65 years old) while we had no age restriction, but yet, in all of these studies, women were older, and had differences in comorbidities compared to men. In ADHF, our results were consistent with a previously published study that used ADHERE (Acute Decompensated Heart Failure National Registry) between 2001 and 2004[10], in both studies there was no significant difference in in-hospital mortality between men and women.

In pneumonia, our study showed that men have worse outcomes than women, unlike a previous study[14] that found that women have worse outcomes for community-acquired pneumonia with 28-day mortality odds ratio of 1.15 (95% CI 1.02–1.30). Howver, our study included all types of pneumonia, and it was consistent with another study that used the Medicare database and showed worse outcomes in men[23].

Limitations and strengths

A limitation of this study is that we used ICD-9 codes for identifying patients. It was not feasible to review charts for such a large number of patients; and therefore, we had to depend on administrative and billing codes. New research using the recent ICD-10 coding is needed to study the consistency of prevalence and implication of comorbidities on early outcomes in hospitalized patients. Another limitation is that we included all patients that were hospitalized in a single regional tertiary center; these patients were from several different states and some from were from other countries. We might have under estimated the mortality or readmission rates if these patients were readmitted to a different hospital closer to their residency place after discharge. Making this less concerning is the fact that we found, gender to be an independent variable from residency place; in addition, we adjusted for residency place (Olmsted County where the hospital is vs. non Olmsted County). Another limitation is that the majority of our included patients were white; our results may not be generalizable to people from other races. Other limitation in our data is that we have included only the first hospitalization; some patients have likely had multiple repeat hospitalizations for the same condition. The strengths of this study include the large sample size, multivariable adjustment and sensitivity analyses to assess robustness of findings.

Clinical and policy implication:

Although this study showed that women hospitalized for ADHF had higher 30 day readmission rate, the absolute risk was small with a number needed to harm of 88 patients (95% CI: 48, 445). For pneumonia, women had lower mortality, with a number needed to harm of 61 patients (95% CI: 36, 202). With this minimal clinically meaningful impact of these differences on the early outcomes of these three important conditions; efforts to address gender difference may need to be diverted towards targeting overall population health, where outcomes of these conditions are still suboptimal in both genders, or towards reducing race/ethnicity disparity, or improving access to care differences.

Conclusion:

Gender disparities interact with comorbidities and impact mortality and readmission. However, this effect varies according to the conditions, seems to be unpredictable and has a minimal meaningful impact on outcomes.

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Contributors: MA conception and design of the study, data collection, data analysis, interpreted results, drafted and revised manuscript; ZW data analysis, manuscript revision and approval of final draft; MHM contributed to study design, manuscript development, approval of final draft; MY: developed the idea for the study, interpreted results, revised manuscript, approval of final draft.

Competing interests: None declared

Ethics approval: Mayo Clinic Institutional Review Committee (IRB).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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Legends:

Table 1: Baseline characteristics

Table 2: Adjusted outcomes

Figure 1: Adjusted outcomes 30 day mortality and 30 day readmission in men vs. women.

Table 1: Baseline characteristics

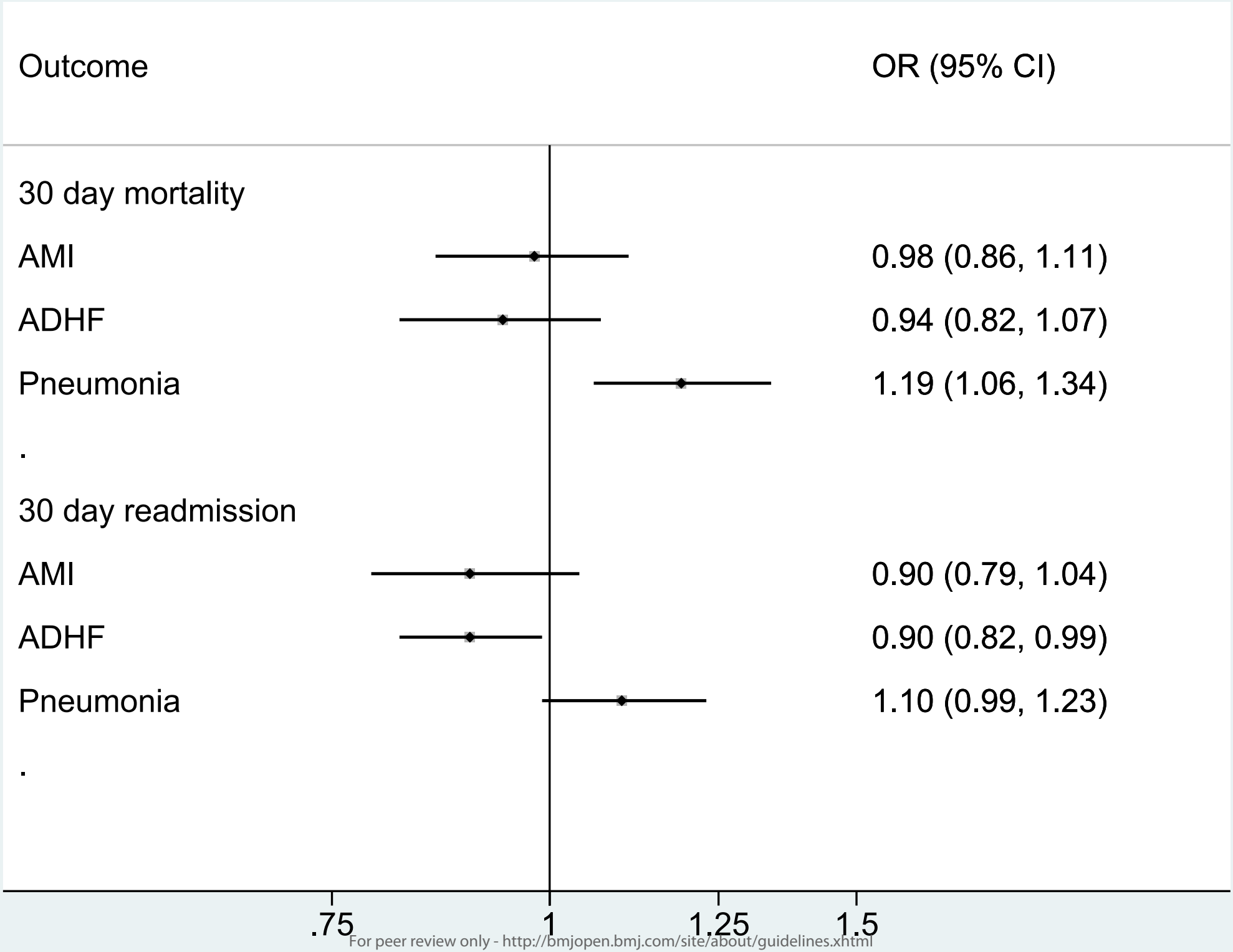
	AMI = 15,777			ADHF =12,265			Pneumonia = 12,929		
	Men 65%	Women 35%	P value	Men 57%	Women 43%	P value	Men 55%	Women 45%	P value
Age (SD)	66.5 (13.3)	73 (13.3)	<0.001	72.3 (13)	75.4 (13.9)	<0.001	69.2 (16.8)	70.8 (17.7)	<0.001
Race %									
Non-white	12.74%	14.12%	0.015	14.25%	14.25%	0.997	15.65%	14.70%	0.14
White	87.26%	85.88%		85.75%	85.75%		84.35%	85.30%	
Comorbidity									
Arthritis	3.37%	5.57%	0.06	4.35%	6.95%	<0.001	4.28%	7.26%	<0.001
Asthma	2.42%	3.89%	<0.001	2.81%	5.25%	<0.001	5.09%	10.31%	<0.001
Dementia	1.73%	3.29%	<0.001	2.65%	4.17%	<0.001	6.9%	8.52%	0.001
Depression	4.4%	6.8%	<0.001	6.28%	9.12%	<0.001	8.64%	12.93%	<0.001
Hypertension	57.64%	65.69%	<0.001	56.52%	62.11%	<0.001	43.91%	48.80%	<0.001
Osteoporosis	0.4%	4.73%	<0.001	0.97%	7.16%	<0.001	2.09%	9.00%	<0.001
Cancer	8.14%	6.95%	0.01	13.42%	11.91%	0.01	25.93%	17.81%	<0.001
Drug abuse	4.15%	1.47%	<0.001	3.65%	0.97%	<0.001	4.54%	2.36%	<0.001
Dyslipidemia	44.46%	40.40%	<0.001	1.06%	27.73%	<0.001	20.54%	17.71%	<0.001
CAD				56.98%	41.27%	<0.001	27.29%	17.78%	<0.001
CHF	21.15%	29.03%	<0.001				20.44%	21.36%	0.20
CKD	9.49%	9.24%	0.60	27.93%	21.62%	<0.001	15.28%	10.71%	<0.001
COPD	11.02%	10.84%	0.73	23.50%	16.67%	<0.001	28.19%	22.8%	<0.001
Diabetes	26.18%	29.62%	<0.001	33.75%	32.31%	0.09	22.78%	19.31%	<0.001
Arrhythmia	25.62%	27.03%	0.06	60.93%	54.23%	<0.001	28.36%	24.80%	<0.001
Stroke	3.35%	4.49%	<0.001	2.84%	2.42%	0.15	2.52%	1.67%	0.001
Length of stay									
Mean (SD)	5.42 (5.83)	5.67 (5.76)	0.01	6.02 (10.22)	5.71 (8.33)	0.07	5.36 (6.01)	5.13 (6.41)	0.04

AA: African American, ADHF: acute decompensated heart failure, AMI: acute myocardial infarction, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: chronic kidney disease, COPD: Chronic Obstructive Pulmonary Disease, NA: Native American, SD: standard deviation.

Table 2: Adjusted outcomes

	AMI		ADHF		Pneumonia	
Men vs. Women	Effect size (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
30 day mortality	OR: 0.98 (0.86 to to 1.11)	0.71	OR: 0.94 (0.82 to 1.07)	0.39	OR: 1.19 (1.06 to 1.34)	0.004
30 day readmission	OR: 0.90 (0.79 to 1.04)	0.16	OR: 0.90 (0.82 to 0.99)	0.03	OR: 1.10 (0.99 to 1.23)	0.08

ADHF: acute decompensated heart failure, AMI: acute myocardial infarction, LOS: length of stay, OR: odds ratio.



Supplementary Table 1: ICD9 codes used in ADHF:

ICD-9	Frequency	%
428	8,665	70.65
428.1	97	0.79
428.2	7	0.06
428.21	305	2.49
428.22	99	0.81
428.23	1,021	8.32
428.3	24	0.2
428.31	243	1.98
428.32	80	0.65
428.33	787	6.42
428.4	6	0.05
428.41	109	0.89
428.42	50	0.41
428.43	742	6.05
428.9	30	0.24
Total	12,265	100

Frequency: Number of patients that were diagnosed based on that code.
%: The percentage of the code out of total number of patients

Supplementary Table 2: ICD9 codes used in AMI.

ICD-9	Frequency	%
410	3	0.02
410.01	536	3.4
410.02	2	0.01
410.1	34	0.22
410.11	2,186	13.86
410.12	11	0.07
410.2	5	0.03
410.21	466	2.95
410.22	3	0.02
410.3	4	0.03
410.31	309	1.96
410.32	2	0.01
410.4	9	0.06
410.41	2,688	17.04
410.42	17	0.11
410.5	4	0.03
410.51	256	1.62
410.52	2	0.01
410.6	1	0.01
410.61	75	0.48
410.7	25	0.16
410.71	8,345	52.89
410.72	58	0.37
410.8	6	0.04
410.81	331	2.1
410.82	2	0.01
410.9	7	0.04
410.91	389	2.47
410.92	1	0.01
Total	15,777	100

Frequency: Number of patients that were diagnosed based on that code.
%: The percentage of the code out of total number of patients

Supplementary Table 3: ICD9 codes used in pneumonia:

ICD-9	Frequency	%
11.6	1	0.01
11.64	1	0.01
52.1	10	0.08
73	2	0.02
115.05	68	0.53
115.95	29	0.22
480	1	0.01
480.1	67	0.52
480.2	1	0.01
480.3	1	0.01
480.8	12	0.09
480.9	57	0.44
481	431	3.33
482	68	0.53
482.1	208	1.61
482.2	163	1.26
482.3	57	0.44
482.31	11	0.09
482.32	6	0.05
482.39	15	0.12
482.4	66	0.51
482.41	140	1.08
482.42	57	0.44
482.49	2	0.02
482.81	8	0.06
482.82	33	0.26
482.83	118	0.91
482.84	46	0.36
482.89	42	0.32
482.9	143	1.11
483	25	0.19
483.8	5	0.04
484.1	3	0.02
484.6	1	0.01
485	104	0.8
486	8,520	65.9
487	234	1.81
495.8	4	0.03
495.9	62	0.48
506	12	0.09
507	2,081	16.1
507.1	6	0.05
507.8	2	0.02
997.32	6	0.05
Total	12,929	100

Frequency: Number of patients that were diagnosed based on that code.
%: The percentage of the code out of total number of patients

Supplementary Table 4: Comorbidities specified by OASH.

Dyslipidemia	Coronary Artery Disease	Depression	COPD
Arthritis	Substance abuse	Diabetes	Dementia
Osteoporosis	Congestive Heart Failure	Cancer	Schizophrenia
Autism	Chronic Kidney Disease	Arrhythmia	Hepatitis
Hypertension	Stroke	Asthma	HIV

Supplementary Table 5: List of ICD-9 codes used for the comorbidities:

The condition	ICD-9 codes used:
Dyslipidemia	272.0, 272.1, 272.2, 272.3, 272.4
Arthritis	714.0, 714.1, 714.2, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.91, 715.92, 715.93, 715.94, 715.95, 715.96, 715.97, 715.98, 720.0, 721.0, 721.1, 721.2, 721.3, 721.90, 721.91
Osteoporosis	733.00, 733.01, 733.02, 733.03, 733.09
Hypertension	401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 362.11, 437.2
Coronary Artery Disease	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.8, 414.9
COPD	490, 491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496
Chronic Kidney Disease	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4
Stroke	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01,434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Depression	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 2 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311
Diabetes	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03,

	250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 366.41
Cancer	Female breast cancer: 174.0, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175.0, 175.9, 233.0, V10.3. Colorectal cancer: 154.0, 154.1, 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 230.3, 230.4, V10.05. Prostate cancer: 185, 233.4, V10.46. Lung cancer: 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 231.2, V10.11.
Arrhythmia	427.31
Asthma	493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
Dementia	331.0, 331.1, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.8, 797

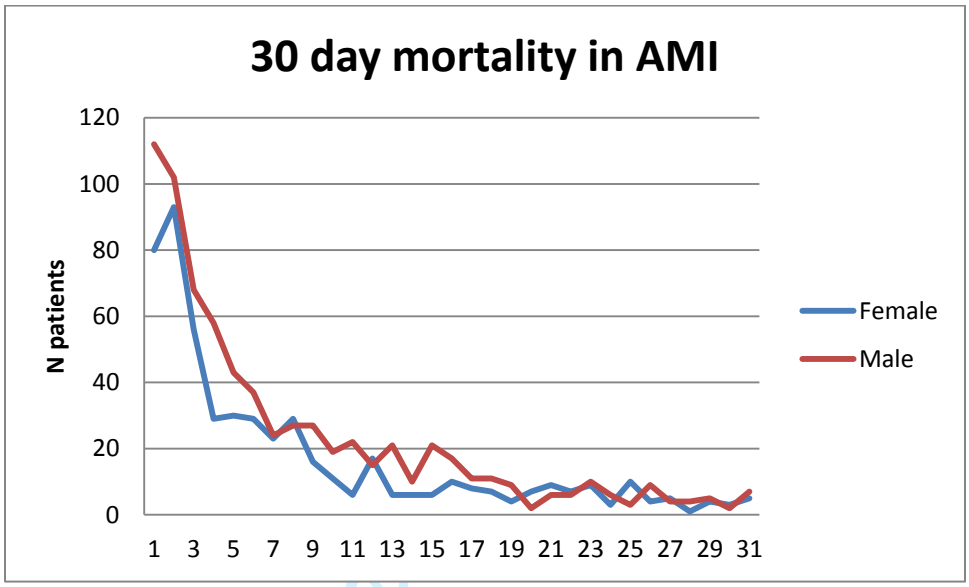
Supplementary Table 6: sensitivity analysis for the last 5 years of the study

Last 5 years	AMI	ADHF	Pneumonia
Men vs. Women	OR (95% CI)	OR (95% CI)	OR (95% CI)
30 day mortality	1.02 (0.73 to 1.43)	0.81 (0.62 to 1.06)	1.12 (0.85 to 1.47)
30 day readmission	0.85 (0.63 to 1.15)	0.78 (0.63 to 0.97)	0.94 (0.74 to 1.20)

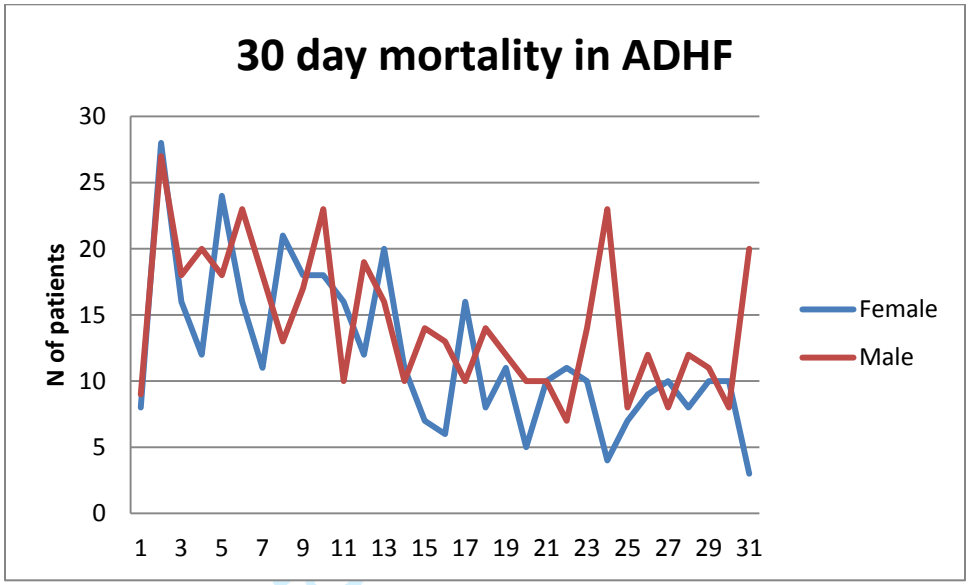
Supplementary Table 7: sensitivity analysis for 15 day mortality and readmission

Last 5 years	AMI	ADHF	Pneumonia
Men vs. Women	OR (95% CI)	OR (95% CI)	OR (95% CI)
15 day mortality	1.00 (0.88 to 1.15)	0.88 (0.73 to 1.05)	1.15 (1.00 to 1.33)
15 day readmission	0.91 (0.81 to 1.03)	0.93 (0.81 to 1.06)	1.10 (0.96 to 1.27)

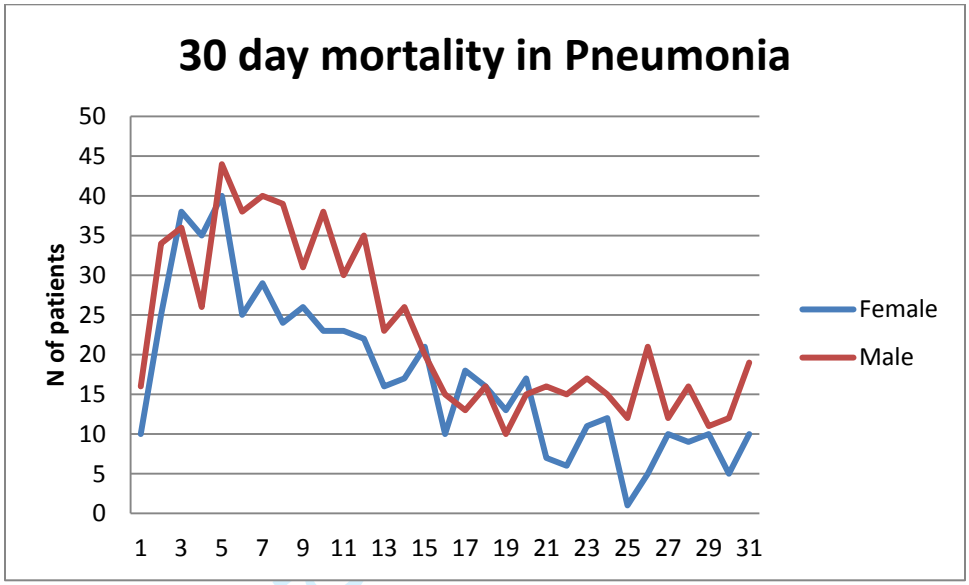
Supplementary Figure 1: 30 day mortality in AMI



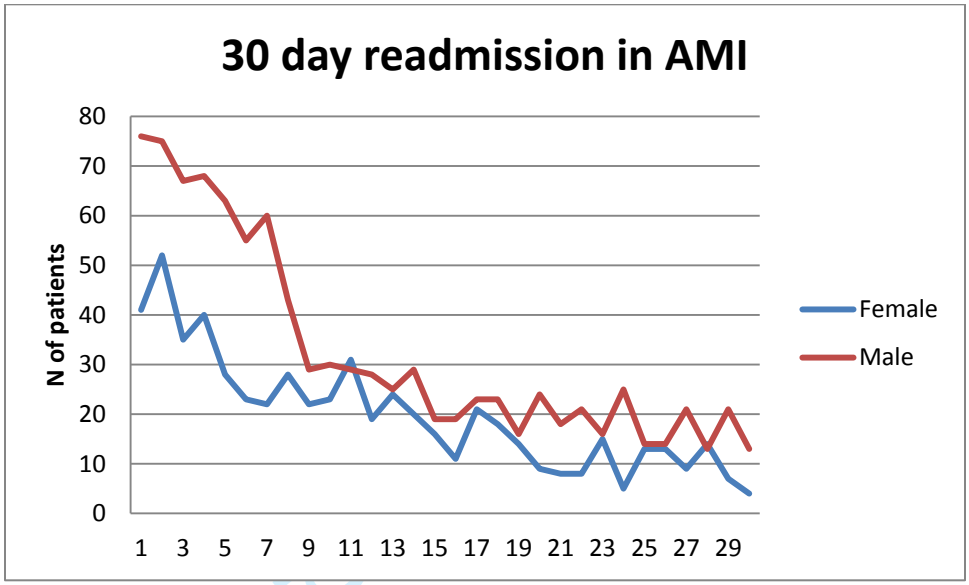
Supplementary Figure 2: 30 day mortality in ADHF



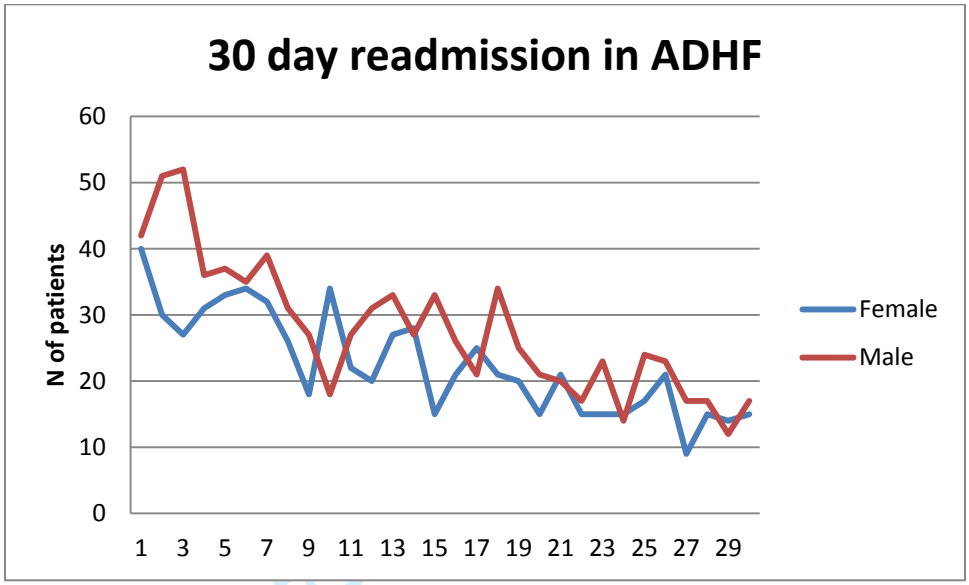
Supplementary Figure 3: 30 day mortality in pneumonia



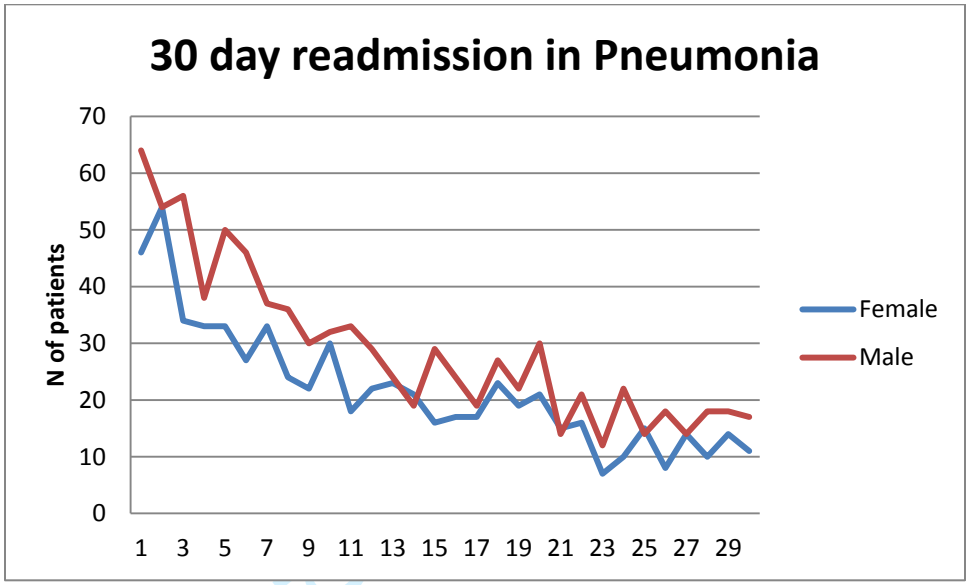
Supplementary Figure 4: 30 day readmission in AMI



Supplementary Figure 5: 30 day readmission in ADHF



Supplementary Figure 6: 30 day readmission in pneumonia



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			**Page number**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*10-12*
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.