Burden of arrhythmias and predictors of mortality among multiple myeloma patients with arrhythmias

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ABSTRACT

Arrhythmias are a major cardiac complication reported among patients with multiple myeloma (MM), but these have not been further characterized in this population. We explored the prevalence of arrhythmias and examined the predictors of mortality among patients with MM with arrhythmias. The National Inpatient Sample data collected between 2016 and 2018 were used to conduct retrospective analyses. Multivariable logistic regression analyses were done to examine the predictors of mortality among patients with MM with arrhythmias. 16.9% of patients with MM reported a diagnosis of any arrhythmias and 70.7% of these were atrial fibrillation. Patients aged 70 years and above had 21% lower odds (adjusted OR (AOR): 0.79; 95% CI: 0.68 to 0.92) of inpatient mortality relative to younger patients. Those in the non-Hispanic black, Hispanic, and non-Hispanic other category were 1.38 (95% CI: 1.16 to 1.64), 1.53 (95% CI: 1.19 to 1.97), and 1.69 (95% CI: 1.29 to 2.21) times more likely to die during hospitalization compared with their counterparts who were non-Hispanic whites. Relative to patients with MM who were on Medicare, those on private (AOR: 1.28; 95% CI: 1.06 to 1.54) and other insurance types (AOR: 1.78; 95% CI: 1.23 to 2.58) had higher odds of mortality. Other predictors of inpatient mortality were elective admission (AOR: 0.67; 95% CI: 0.52 to 0.85) and Charlson comorbidity indices between 5–7 (AOR: 1.23; 95% CI: 1.07 to 1.41) and ≥8 (AOR: 1.45; 95% CI: 1.21 to 1.73) compared with comorbidity indices between 0 and 4. Our study adds to the body of knowledge on the need for proper diagnosis and management of cardiac arrhythmias in patients with MM. Research is needed to further assess the time of arrhythmia diagnosis and its impact on health outcomes among patients with MM.

Significance of this study

What is already known about this subject?

- Patients with multiple myeloma have risk factors for adverse cardiovascular outcomes including arrhythmias.

What are the new findings?

- Age, race/ethnicity, insurance type, admission type and comorbidities predict mortality among patients with multiple myeloma with arrhythmias.

How might these results change the focus of research or clinical practice?

- Our findings suggest that there may be a role for arrhythmia surveillance among patients with risk factors; however, further research is needed to assess the impact of time of arrhythmia diagnosis on health outcomes in patients with multiple myeloma.

INTRODUCTION

Multiple myeloma (MM) is a type of blood cancer affecting plasma cells.[1] It is the second most common hematological malignancy which is associated with significant morbidity.[2] It occurs due to abnormal proliferation of plasma cells in the bone marrow.[1] It has an incidence rate of 2.1 per 100,000 persons, with the highest incidence found in North America and western Europe.[3] MM represents about 2.1 million disability-adjusted life years worldwide in 2016.[3] The clinical presentation of MM includes bone pain, hypercalcemia, anemia, renal failure, and cardiac abnormalities.[4] With the burden of the disease and advancement in science, novel therapies have been designed to treat and prolong life for patients with MM.[5]

Due to progress made in treatment of MM with chemotherapy and stem cell transplantation in those eligible, mortality rates have reduced with an overall 5-year survival rate of 54%.[6] Most patients diagnosed with MM are the elderly aged 65 years and above.[7] As a result of their age and other factors, many patients with a diagnosis of MM have predisposing cardiovascular risk factors placing them at risk for adverse cardiovascular outcomes.[8] MM affects cardiac function as excessive production of immunoglobulins from plasma cells can lead to deposition of these proteins in several organs of the body including the heart.[9] Associated cardiac complications include thromboembolic disorders, arrhythmias, cardiomyopathies, and heart failure.[8 10]

Cardiac arrhythmias are a major cardiac complication in patients with MM.[11] Risk factors for arrhythmias in patients with MM include amyloidosis, the elderly, chronic anemia, hyper viscosity, electrolyte imbalance, toxic effects of related chemotherapy, patients with recent stem cell transplant and underlying comorbidities.[12] Few studies have been conducted to evaluate the burden of arrhythmias in patients with MM.[11 12] Research by Shah *et al* using a nationwide dataset found about 20% of patients with MM to have arrhythmias, higher than the general population where arrhythmias are reported in 13.8%.[12] Multiple factors have been shown to be associated the high incidence of arrhythmias in patients with MM, which include cardiac amyloidosis, older age, co-existing cardiovascular conditions, treatment of cardiac diseases, use of chemotherapeutic agents, electrolyte abnormalities, and autologous stem cell transplantation.[8 10 12–15]

However, research has not been done to further assess mortality among patients with MM with arrhythmias. To better characterize arrhythmias in this population, we conducted a retrospective study using the National Inpatient Sample (NIS) database from 2016 to 2018. We examined the prevalence of arrhythmias and the predictors of mortality among patients with MM who have arrhythmias. Additionally, we evaluated the association between mortality and different comorbidities among patients with arrhythmias. This study sought to assess the burden of arrhythmias among patients with MM and increase awareness of physicians on the health outcomes in this population related to different arrhythmias.

MATERIALS AND METHODS

Data source

The Healthcare Cost and Utilization Project NIS data collected between 2016 and 2018 were used for all analyses. This is the largest, publicly available all-payer inpatient care database in the USA. It is sponsored by the Agency for Healthcare Research and Quality. The collected data covers approximately 20% stratified sample of all discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals. This covers over 95% of all US admissions after proper weights are applied. The International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes were used to document the clinical data which also contains demographic information, insurance type, total charges, procedures, severity and comorbidity measures, hospital-level and clinical information about patients. Further detailed information on the study design, methodology, and data collection is described elsewhere.[16 17]

Study population

The following ICD-10 codes: C90.0 (MM), C90.00 (MM not having achieved remission), C90.01 (MM in remission), and C90.02 (MM in relapse) were used to identify patients with a diagnosis of MM and included in all analyses.

Measures

Arrhythmias

Based on previously published literature, ICD-10 codes were used to identify patients with a diagnosis of arrhythmias including atrial fibrillation (I48), ventricular fibrillation (I49.01, I49.02), ventricular tachycardia (I47.2), supraventricular tachycardia (I47.1), premature atrial/ventricular depolarization (I49.1, I49.3), SA node dysfunction (427.81), and cardiac arrest (I46.2, I46.8, and I46.9).

Mortality

The NIS data contain information about inpatient mortality representing patients who died during hospitalization. The mortality variable was categorized into 'died' versus 'not died'.

Covariates

Variables included in the analyses are sociodemographic (age, gender, race/ethnicity, median household national income quartiles, insurance type), hospital-level (hospital region, hospital location), and clinical information (patient disposition, admission type, length of stay, Charlson Comorbidity Index). Individual comorbidities included in the analyses were acute myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease, cerebrovascular disease (CVD), dementia, chronic obstructive pulmonary disease (COPD), rheumatoid disease, diabetes mellitus, renal disease, and metastatic cancer.

Statistical analyses

Sociodemographic, hospital-level, and clinical characteristics were explored by arrhythmia status with Pearson's χ^2 statistics used to assess for statistical significance. The survey command was used to assess the weighted proportions of arrhythmias and arrhythmia subtypes. Univariate and multivariable logistic regression analyses were used to examine the predictors of inpatient mortality among patients with MM with arrhythmias. Furthermore, univariate and multivariable logistic regression analyses were used to examine the association between inpatient mortality and the different comorbidities among patients with arrhythmias. All analyses were conducted using Stata V.16.1. The Wald test was used to determine statistical significance with a two-sided p value <0.05.

RESULTS

Out of 68 279 hospitalizations, 16.9% reported a diagnosis of arrhythmias. Of those with arrhythmias, 70.7% had atrial fibrillation, 10.5% had supraventricular tachycardias, and 7.6% had ventricular tachycardias (table 1). Among those with arrhythmias, the majority were male (60.9%); 71.9%

Table 1 Arrhythmia burden/Prevalence among hospitalized patients with multiple myeloma

Type	Wt %
Any arrhythmia	16.89
Atrial fibrillation	70.74
Ventricular fibrillation	0.42
Ventricular tachycardia	7.62
Supraventricular tachycardia	10.48
Premature atrial/Ventricular depolarization	5.04
Cardiac arrest	5.70

Type, arrhythmia type; Wt%, weighted percentages.

were non-Hispanic whites (71.9%); 70% were aged 70 years and above, and 81% were on Medicare. While 72.3% of them were hospitalized in urban teaching hospitals, about 90% of those admissions were non-elective; 51% of the hospitalized patients were discharged to facilities/home healthcare and more than half of the arrhythmic patients had a length of stay of 5 days or less (table 2).

Adjusted analyses of predictors of mortality among hospitalized patients with MM with arrhythmias showed that those aged 70 years and above had 21% lower odds (adjusted OR (AOR): 0.79; 95% CI: 0.68 to 0.92) of inpatient mortality relative to younger patients. Those in the non-Hispanic black, Hispanic, and non-Hispanic other category were 1.38 (95% CI: 1.16 to 1.64), 1.53 (95% CI: 1.19 to 1.97), and 1.69 (95% CI: 1.29 to 2.21) times more likely to die during hospitalization compared with their counterparts who were non-Hispanic whites. Relative to patients with MM who were on Medicare, those on private (AOR: 1.28; 95% CI: 1.06 to 1.54) and other insurance types (AOR: 1.78; 95% CI: 1.23 to 2.58) had higher odds of mortality. Furthermore, patients with MM who were electively admitted were 33% less likely (AOR: 0.67; 95% CI: 0.52 to 0.85) to die during hospitalization compared with patients with MM admitted non-electively. When compared with patients with Charlson comorbidity indices of 0–4, those with indices between 5 and 7 were 1.23 times more likely (95% CI: 1.07 to 1.41) while patients with MM with Charlson comorbidity indices of 8 or greater were 1.45 times more likely (95% CI: 1.21 to 1.73) to die during hospitalization. Sex, household income, hospital region, hospital location, and length of stay did not predict inpatient mortality (table 3).

Adjusted analyses of the comorbidities predicting mortality among patients with MM with arrhythmias showed that patients with acute MI had 1.5 times higher odds (AOR: 1.55; 95% CI: 1.31 to 1.82) of inpatient mortality compared with those without acute MI. Patients with CVD also had 1.5 times (AOR: 1.54; 95% CI: 1.24 to 1.92) higher odds of death during hospitalization relative to those without CVD. Furthermore, renal disease (AOR: 1.16; 95% CI: 1.02 to 1.32) and metastatic cancer (AOR: 1.52; 95% CI: 1.17 to 1.98) were associated with higher odds of mortality among patients with MM with arrhythmias. CHF, peripheral vascular disease, dementia, COPD, and diabetes mellitus did not predict inpatient mortality in these patients (table 4).

DISCUSSION

In our study about 17% of patients with MM had arrhythmias. Majority of the patients with MM who had arrhythmias were males, 70 years and above, and non-Hispanic whites. These patients were non-electively admitted in urban hospitals, and had higher hospital stays. We found older age, race/ethnicity, insurance status, admission type, and Charlson Comorbidity Index to predict mortality among patients with MM with arrhythmias. Furthermore, we noted that acute MI, CVD, renal disease, and metastatic cancer predicted higher inpatient mortality among these patients while CHF, peripheral vascular disease, dementia, COPD, and diabetes mellitus did not predict inpatient mortality.

Table 2 Characteristics of hospitalized patients with multiple myeloma in the National Inpatient Sample between 2016 and 2018

	Wt%		
	Arrhythmia		
	Yes	No	
	N=11,529	N=56,750	P value
Age (years)			<0.001
<70	30.03	52.29	
70 and above	69.97	47.71	
Gender			<0.001
Male	60.87	54.32	
Female	39.13	45.68	
Race/Ethnicity			<0.001
Non-Hispanic white	71.91	61.94	
Non-Hispanic black	17.33	23.20	
Hispanic	5.91	8.95	
Non-Hispanic other	4.85	5.91	
Median household income national quartiles			<0.001
Quartile 1	23.37	27.47	
Quartile 2	24.35	24.76	
Quartile 3	26.26	24.39	
Quartile 4	26.02	23.37	
Insurance type			<0.001
Medicare	80.99	65.70	
Medicaid	3.18	7.04	
Private	13.64	23.73	
Other	2.20	3.53	
Hospital region			<0.001
Northeast	20.11	21.03	
Midwest	25.46	22.6	
South	35.47	38.57	
West	18.96	17.80	
Hospital location			<0.001
Rural	6.13	6.40	
Urban non-teaching	21.54	18.47	
Urban teaching	72.33	75.12	
Patient disposition			<0.001
Routine	38.23	54.01	
Transfer to facility/ Home healthcare	51.15	41.63	
Died	10.63	4.36	
Mortality			<0.001
No	89.75	96.29	
Yes	10.25	3.71	
Admission type			<0.001
Elective	10.11	17.22	
Non-elective	89.89	82.78	
Length of stay			<0.001
5 days or less	51.03	58.14	
>5 days	48.97	41.86	
Charlson Comorbidity Index			<0.001
0–4	43.91	62.70	
5–7	40.77	25.99	
≥8	15.33	11.31	

N, unweighted number of observations; Wt%, weighted percentages.

Table 3 Factors associated with mortality among hospitalized patients with multiple myeloma with arrhythmias

	OR (95% CI)	
	Unadjusted	**Adjusted**
Age (years)		
<70	Reference	Reference
70 and above	**0.70 (0.62 to 0.80)**	**0.79 (0.68 to 0.92)**
Gender		
Male	Reference	Reference
Female	0.91 (0.81 to 1.04)	0.92 (0.81 to 1.05)
Race/Ethnicity		
Non-Hispanic white	Reference	Reference
Non-Hispanic black	**1.52 (1.30 to 1.78)**	**1.38 (1.16 to 1.64)**
Hispanic	**1.66 (1.31 to 2.10)**	**1.53 (1.19 to 1.97)**
Non-Hispanic other	**1.80 (1.37 to 2.36)**	**1.69 (1.29 to 2.21)**
Median household income national quartiles		
Quartile 1	Reference	Reference
Quartile 2	1.01 (0.84 to 1.20)	1.11 (0.92 to 1.33)
Quartile 3	0.84 (0.70 to 1.00)	0.92 (0.76 to 1.12)
Quartile 4	1.01 (0.70 to 1.00)	1.15 (0.95 to 1.39)
Insurance type		
Medicare	Reference	Reference
Medicaid	**1.50 (1.10 to 2.06)**	1.09 (0.78 to 1.53)
Private	**1.40 (1.18 to 1.65)**	**1.28 (1.06 to 1.54)**
Other	**1.95 (1.37 to 2.75)**	**1.78 (1.23 to 2.58)**
Hospital region		
Northeast	Reference	Reference
Midwest	0.97 (0.81 to 1.17)	0.97 (0.79 to 1.17)
South	1.05 (0.89 to 1.25)	0.99 (0.83 to 1.18)
West	1.18 (0.97 to 1.42)	1.14 (0.94 to 1.39)
Hospital location		
Rural	Reference	Reference
Urban non-teaching	0.94 (0.71 to 1.25)	0.89 (0.65 to 1.21)
Urban teaching	1.09 (0.84 to 1.42)	0.99 (0.74 to 1.32)
Admission type		
Non-elective	Reference	Reference
Elective	**0.69 (0.55 to 0.87)**	**0.67 (0.52 to 0.85)**
Length of stay		
5 days or less	Reference	Reference
>5 days	1.12 (0.99 to 1.26)	1.09 (0.96 to 1.23)
Charlson Comorbidity Index		
0–4	Reference	Reference
5–7	**1.24 (1.08 to 1.42)**	**1.23 (1.07 to 1.41)**
≥8	**1.49 (1.26 to 1.76)**	**1.45 (1.21 to 1.73)**

Model adjusted for age, gender, race/ethnicity, median household income national quartiles, hospital region, hospital location, Charlson Comorbidity Index, insurance type, admission type, and length of stay. Boldface indicates statistical significance.

Table 4 Comorbidities that predict mortality among hospitalized patients with multiple myeloma with arrhythmias

	OR (95% CI)	
	Unadjusted	**Adjusted**
Acute myocardial infarction	**1.59 (1.37 to 1.85)**	**1.55 (1.31 to 1.82)**
Congestive heart failure	1.07 (0.95 to 1.21)	1.02 (0.89 to 1.16)
Peripheral vascular disease	0.91 (0.75 to 1.10)	0.86 (0.70 to 1.06)
Cerebrovascular disease	**1.52 (1.23 to 1.87)**	**1.54 (1.24 to 1.92)**
Dementia	0.94 (0.74 to 1.20)	1.02 (0.79 to 1.31)
COPD	**0.82 (0.72 to 0.95)**	0.87 (0.75 to 1.01)
Rheumatoid disease	**0.41 (0.24 to 0.69)**	**0.44 (0.26 to 0.76)**
Diabetes mellitus	0.97 (0.82 to 1.14)	0.94 (0.80 to 1.12)
Renal disease	1.11 (0.98 to 1.25)	**1.16 (1.02 to 1.32)**
Metastatic cancer	**1.53 (1.19 to 1.97)**	**1.52 (1.17 to 1.98)**

Model adjusted for age, gender, race/ethnicity, median household income national quartiles, hospital region, hospital location, and insurance type. Boldface indicates statistical significance.
COPD, chronic obstructive pulmonary disease.

The risk of arrhythmia increases with age, similar to our patients with MM.[18] Older age was found to be associated with lower odds of arrhythmia-related mortality possibly because these patients are dying from other causes. A study conducted among elderly patients with MM observed the most common causes of death in this population to be infection, heart failure, and renal failure.[19] However, arrhythmias were not examined in this study. A recent study by Wang *et al* that showed that patients with MM who had heart rate >100 (though did not specify if they were arrhythmias) reported a higher all-cause mortality in patients who were <75 years old compared with those >75 years. These findings may be because age-related cardiovascular comorbidities attenuated the effect in this age group.[20]

Age is a known independent risk factor for arrhythmias,[21 22] and in this population of patients, many have underlying cardiovascular diseases.[8] About 63% of patients with newly diagnosed MM were found to have cardiac events prior to diagnosis with arrhythmia being most frequent.[23] The exact mechanism of arrhythmias in patients with MM is not known. Arrhythmias in patients with MM might be related to treatment side effects that have been reported with the use of proteasome inhibitors, immunomodulatory agents, and hematopoietic stem cell transplant.[24–27] It might also be due to deposition of amyloid or light chain in the heart which increases the risk of cardiac dysfunction.[28]

Compared with non-Hispanic whites, other minority patients with MM had higher risk of arrhythmia-related mortality. While some studies suggest inferior MM- related survival among blacks,[29 30] there is evidence that blacks and Hispanics receive novel therapies later than their white counterparts.[31] These disparities may be persisting in arrhythmia care, although there are no specific studies that have reported on this. Electively admitted patients with MM had lower odds of inpatient mortality probably because they were less sick and more likely admitted for planned procedures such as chemotherapy.[32] Patients with MM with arrhythmias on private and other insurance types had significantly higher odds of mortality. More research is needed to further explain these findings.

Atrial fibrillation was the most common type of arrhythmia identified and supraventricular tachycardia was the second most common type of arrhythmia. This is similar to the findings by Shah *et al*.[12] The burden of arrhythmias in patients with MM has been reported to be as high as 50% in a study.[11] MM has been reported to be associated with incident atrial fibrillation,[33] and patients with MM with atrial fibrillatio were shown to have an increase in all-cause

mortality.[20] These findings are similar to what was reported in our study.

Our study also showed that patients with MM who had arrhythmias had a higher Charlson Comorbidity Index. A study in Sweden found higher comorbidities in patients with MM with an associated increased risk of death in those with arrhythmias.[34] On further analyses of comorbidities associated with inpatient mortality among patients with MM with arrhythmias, acute MI, CVD, renal disease, and metastatic cancer were found to predict higher inpatient mortality. These comorbidities increase their risk of arrhythmias and mortality independently of having MM and might explain the higher predicted mortality in this subgroup of patients.[35–37] Conditions such as acute MI, CVD, renal disease, and metastatic cancer usually present acutely, frequently requiring admission. This might lead to increased inpatient mortality in these groups of patients. On the other hand, peripheral vascular disease, dementia, COPD, DM are chronic conditions with long-term progression and probably no direct effect on inpatient mortality, although it may affect overall mortality. While CHF is a possible cardiovascular complication in patients with MM, we did not see it predict mortality maybe because of the heterogeneity of CHF which encompasses a large group of people with several stages of the disease.

A major strength of the study is the use of a large national database that is representative of the general US population. We also had a large sample size giving us the statistical power for analysis of the data. Despite these, we had some limitations. The NIS database used for this study only contains inpatient data, hence we were unable to assess any outcomes post hospital discharge. Furthermore, these data capture every hospital discharge as a distinct observation, so re-admissions could not be accounted for. ICD-10 codes were used to identify the different diagnoses evaluated in the study and there is a likelihood of missing diagnostic or procedure codes. Also, we could not ascertain the time of incident diagnosis of arrhythmias. Therefore, we were not able to further categorize if the diagnosis of arrhythmias was prior to diagnosis or treatment for MM. Due to the type of data, we are not able to confirm when patients became diagnosed with the comorbid conditions examined, whether it was prior to or after MM diagnosis. Regardless, our study is novel and adds to the body of knowledge on the need for proper diagnosis and management of cardiac arrhythmias in patients with MM. Screening of patients diagnosed with MM for arrhythmias pre-treatment and post-treatment should be considered.

In conclusion, we examined the burden of arrhythmias and predictors of inpatient mortality among patients with MM with arrhythmias. We found that older age was associated with lower odds of inpatient mortality. While non-Hispanic blacks, and Hispanics were more likely to die during hospitalization compared with their white counterparts, patients with MM on private and other insurance types also had higher odds of inpatient mortality relative to Medicare patients. Acute MI, CVD, renal disease, and metastatic cancer were the comorbidities identified to predict inpatient mortality in this population. Additionally, elective admission was related to lower in-hospital mortality compared with non-elective admission. These findings suggest that there may be a role for surveillance and aggressive management of arrhythmias in patients with MM, especially when they have identified risk factors for mortality. Research is needed to further assess the time of arrhythmia diagnosis and its impact on health outcomes among patients with MM.

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