Autonomous Mortality Risk Linked to Anemia Post Myocardial Infarction in Patients with and Without Diabetes

Anand Shankar

Associate Professor, Department of Medicine, Netaji Subhas Medical College and Hospital, Bihta, Patna, Bihar, India

Abstract

Introduction: Anemia and diabetes mellitus are recognized as significant risk characteristics contributing to increased short-term mortality rates subsequent to an acute myocardial infarction (AMI). The prevalence of anemia is higher among individuals diagnosed with diabetes mellitus. A retrospective study was conducted to evaluate the effects of the coexistence of diabetes along with anemia on outcomes following myocardial infarction.

Methods: Data from a comprehensive registry covering the entire population were obtained for a cohort of consecutive AMI hospital admissions. The study categorized patients into four categories based on diabetes and anemia presence: Category 1 (8 patients with both), Category 2 (17 patients with diabetes but no anemia), Category 3 (9 patients with anemia but no diabetes), and Category 4 (40 patients with neither). The study focused on two primary outcome measures: mortality rates at 30 days and from 31 days to 36 months.

Results: At 30 days, mortality rates were: Category 1 (31.3%), Category 2 (15.1%), Category 3 (20.5%), and Category 4 (5.6%). From 31 days to 36 months, mortality rates were: Category 1 (46.6%), Category 2 (21.8%), Category 3 (33.3%), and Category 4 (11.4%). Diabetes as well as anemia continued separate risk characteristics for 36-month mortality, with odds ratios of 1.51 and 1.49, respectively. Cardiovascular deaths from 31 days to 36 months accounted for 42.7% in Category 1, 53.1% in Category 2, 46.0% in Category 3, and 49.8% in Category 4.

Conclusion: The coexistence of diabetes and anemia in patients is related with a markedly elevated mortality rate when compared to individuals with either diabetes as well as anemia in isolation. Cardiovascular mortality continued to be the predominant cause of death across all cohorts.

Keywords: Diabetes, Anemia, Acute Myocardial Infarction.

Introduction

Both anemia as well as diabetes mellitus (DM) are acknowledged as robust and autonomous indicators of risk for death and recurrent ischemia subsequent to acute myocardial infarction (AMI) [1]. The prevalence of anemia is significantly higher in people diagnosed with DM as compared those having no DM, with a relative risk of 2-3 times. This association remains significant even after adjusting for GFRs and iron stores [2]. Recent research findings have indicated that the presence of anemia in individuals diagnosed with ischemic heart disease (IHD) is correlated with a heightened risk of short-term mortality. Limited knowledge exists regarding the extended-term survival outcomes of individuals diagnosed with IHD and comorbid anemia. A single study indicated that there was no discernible disparity in long-term mortality rates associated with anemia after accounting for various confounding factors [3]. Given that anemia frequently serves as an indicator of an underlying pathological condition, the precise etiologies of mortality linked to a diminished hemoglobin concentration remain elusive. It is plausible that these patients may be succumbing to a comorbid condition rather than cardiovascular disease. Moreover, the investigation regarding the prognosis of individuals with acute myocardial infarction (AMI) who present with both anemia and diabetes remains lacking in current medical literature.

Hence, the present investigation was led to estimate the influence of anemia on the morbidity and mortality outcomes, both in the short and long term, among individuals who have experienced an AMI, with and without DM. Additionally, the study aimed to ascertain the specific causes of mortality within this particular patient population.

Methods

Study setting, design and population: Thorough clinical information were collected through chart audits from adult care hospitals in Bihar, India for patients admitted with AMI for 3 years. Participants were categorized into 4 category based on the

presence or absence of anemia and diabetes on admission.

Data Elements: The analyzed dataset consisted of patient demographics and clinical characteristics, which encompassed gender, age, BMI, BP, type of AMI, tobacco use, familial history of CVD, previous instances of AMI or a history of congestive heart failure, treatments given during being hospitalized, cardiac drugs used upon the discharge process, rates of mortality, and re-admissions for re-infarction, uncontrolled angina, congestive heart failure, or AMI. The laboratory results encompassed the mean glucose concentration upon enrollment, the hemoglobin concentration upon enrollment, the profile of lipids, the serum creatinine kinase concentration, and the serum creatinine concentration. The determination of the clearance of creatinine was conducted employing the Cockroft-Gault equation.

Outcomes of Interest: The evaluated outcomes encompassed mortality within a 30-day timeframe and extended up to 36 months. Additionally, the occurrence of readmission due to unstable angina, non-fatal MI, or congestive heart failure was assessed. A composite measure combining all 3 morbidity endpoints was also considered. Furthermore, the cause of death within the specified 30-day and 36-month periods was examined.

Data Analysis: The clinical and demographic features of the study categories were assessed by employing analysis of variance (ANOVA) for continuous parameters and chi-square analyses for categorical variables. The statistical analyses were performed utilizing SPSS 10.0 software (Chicago, IL).

Results

A total of 75 patients were admitted presenting with acute myocardial infarction (MI). As a consequence of insufficient data, four patients had been excluded from the analysis that followed. A total of 74 patients (98.5%) were enrolled in the study and subsequently monitored for a maximum duration of 36 months starting from their initial hospitalization. The patients were categorized into four distinct category based on their anemia and diabetes status. Category 1 consisted of patients with both diabetes mellitus (DM) and anemia, with a total of 8 individuals. Category 2 included patients with DM but without anemia, with a total of 17 individuals. Category 3 comprised patients without DM but with anemia, with a total of 9 individuals. Lastly, Category 4 consisted of patients without DM and without anemia, with a total of 40 individuals.

Baseline Characteristics: The incidence of anemia in patients with diabetes mellitus (DM) was found to be 26.4%, whereas in the non-DM category, it was observed to be 16.9%. The prevalence of anemia was observed to be higher among the elderly population in both the cohorts of patients with diabetes and those without diabetes. Patients diagnosed with anemia exhibited diminished creatinine clearances, as evidenced by the following values: category 1 (38.2 mL/min), category 2 (60.4 mL/min), category 3 (40.5 mL/min), and category 4 (63.6 mL/min). The majority of patients diagnosed with anemia presented with a non-ST elevation myocardial infarction (MI) upon admission. Specifically, 71.7% of patients in Category 1 and 66.7% of patients in Category 3 fell into this category. Conversely, patients without anemia were more prone to experiencing an ST-elevation MI. In Category 2, 37.9% of patients had an ST-elevation MI, while in Category 4, this figure was 42.2%.

Cardiac Risk Factors: The aforementioned details have been succinctly presented in Table 1. The prevalence of family history of premature coronary artery disease was observed to be lower among patients diagnosed with anemia. Specifically, the percentages of patients with family history in categories A, C, B, and D were 10.7%, 12.1%, 18.6%, and 31.2%, respectively. The prevalence of prior myocardial infarction (MI) was observed to be higher in category 1 (33.0%), category 2 (25.1%), category 3 (26.3%), and category 4 (16.9%). Similarly, the occurrence of congestive heart failure (CHF) was found to be significantly elevated in category 1 (26.9%), category 2 (11.0%), category 3 (17.8%), and category 4 (3.8%). These findings indicate a notable association between the presence of anemia, diabetes, or both, and an increased likelihood of experiencing previous MI or CHF. A higher proportion of patients diagnosed with DM exhibited a preexisting medical condition of hypertension across the different categories (category 1: 62.3%, category 2: 60.4%, category 3: 50.4%, and category 4: 42.7%).

Table 1: Cardiac Risk Factors

	Category 1 Diabetes Anemia n = 8	Category 2 Diabetes No Anemia n = 17	Category 3 No Diabetes Anemia n = 9	Category 4 No Diabetes No Anemia n = 40
Family History of CAD (%)	10.7	18.6	12.1	31.2
Smoker or ex-smoker (%)	55.4	62.9	58.7	68.2
Previous	62.3	60.4	50.4	42.7

Diagnosis HTN (%)				
Previous MI (%)	33.0	25.1	26.3	16.9
Previous CHF (%)	26.9	11.0	17.8	3.8

Outcome Findings: The calculation of all-cause mortality was performed in a distinct manner, taking into account mortality occurring within a span of 30 days following admission, as well as mortality occurring between 31 days and 36 months post-admission. This approach was adopted to encompass both immediate and prolonged outcomes. The short-term all-cause mortality rates were observed as follows: 31.3% in category 1, 15.1% in category 2, 20.5% in category 3, and 5.6% in category 4. The observed long-term mortality rates were as follows: 46.6% in category 1, 21.8% in category 2, 33.3% in category 3, and 11.4% in category 4. Regarding morbidity, there was an absence of disparity observed in the composite endpoint encompassing hospitalization due to non-fatal re-infarction, congestive heart failure (CHF), and/or unstable angina between the two categories within a 30-day timeframe. In the time span ranging from 31 days to 36 months, it was observed that category 2 exhibited the highest incidence of events. This finding holds significance when comparing it to the non-diabetic categories, namely category 1 (22.0%), category 3 (19.8%), and category 4 (21.1%). Upon analyzing the discrete elements of morbidity within the timeframe of 31 days to 36 months, no statistically substantial disparities were detected in the frequencies of hospital admissions attributed to non-fatal reinfarction. The incidence of congestive heart failure (CHF) admissions was found to be highest among patients presenting with comorbidities of diabetes and anemia. Specifically, the prevalence rates were as follows: 11.0% in category 1, 5.7% in category 2, 7.2% in category 3, and 1.9% in category 4. In the context of unstable angina, it was observed that patients diagnosed with anemia exhibited elevated rates of readmission. Specifically, the readmission rates for category 1, category 2, category 3, and category 4 were recorded as 6.7%, 14.2%, 11.6%, and 15.8%, respectively.

Cause of Death: At the 30-day mark, the predominant cause of mortality among patients was cardiovascular disease, with a notable prevalence observed across all categories: category 1 (72.2%), category 2 (81.6%), category 3 (72.8%), and category 4 (84.9%). At the 36-month mark, cardiovascular death continued to be the predominant cause of mortality across all categories (category 1: 42.7%, category 2: 53.1%, category 3: 46.0%, and category 4: 51.8%). However, it is noteworthy that between 50% and 60% of deaths were now attributed to competing etiologies across the various categories. The cohort denoted as category 3 exhibited a notably elevated mortality rate attributed to cancer within a span of 30 days (6.0%), in comparison to category 1 (2.7%), category 2 (0.0%), and category 4 (0.7%). However, at the 36-month mark, the observed disparity exhibited a diminished level of statistical significance. Despite observing a higher 30-day mortality rate attributed to gastrointestinal (GI) causes in both anemia categories (category 1: 2.5% and category 3: 3.7%) compared to category 2 (0.4%) and D (0.7%), no significant disparity in death due to GI-disease was detected at the 36-month mark.

Discussion

The present study serves to enhance our comprehension of the mortality risks, both immediate and prolonged, in individuals diagnosed with AMI. The study aimed to achieve two primary objectives: firstly, to evaluate the collective influence of anemia and diabetes on AMI outcomes, and secondly, to ascertain the precise etiologies of mortality associated with anemia. The present study substantiates anemia as a distinct and autonomous risk factor for mortality following MI, thereby corroborating existing evidence. However, it is noteworthy that our findings deviate from prior investigations in this field. Recent reports have postulated a connection between anemia and short-term mortality. However, our data analysis reveals that anemia is primarily related with an amplified risk of long-term mortality. One potential explanation for this observed discrepancy could be attributed to divergences in the design of the studies and the criteria used to define anemia. In previous studies, it has been reported that there exists a negative correlation between hematocrit levels and the mortality rate within a span of 30 days among elderly patients covered by Medicare. However, it is important to note that this correlation was not adjusted for any confounding factors [4]. In contrast, the study conducted by Sabatine *et al.* observed a notable rise in cardiovascular mortality exclusively when hemoglobin levels declined below 110 g/L [1]. Conversely, our investigation established the criteria for anemia as hemoglobin levels below 120 g/L in females and below 130 g/L in males. The findings of our analysis indicate that the influence of anemia on survival exhibited the greatest prominence within the lowest quintile of hemoglobin levels, irrespective of gender and diabetes status. The absence of a discernible disparity in immediate mortality could potentially be attributed to the incorporation of instances of mild anemia, wherein the consequential effects on short-term results may have been negligible. This inclusion may have inadvertently obscured the assessment of mortality hazard in cases of severe anemia.

An alternative hypothesis for the observed disparity could potentially be attributed to variances in transfusion frequencies across different cohorts. A recent report has indicated the possibility of adverse effects associated with blood transfusions in cases of acute coronary syndrome [5]; however, there is a dearth of available data regarding the frequency of transfusions in such instances.

Within the scope of our investigation, it was observed that the mortality rate at the 36-month mark exhibited a notable and statistically significant escalation in both cohorts afflicted with anemia. The coexistence of diabetes and anemia presents a significant mortality hazard within a span of 36 months, as approximately 65% of individuals experience fatal outcomes during this period. Multiple etiological factors may potentially contribute to the observed increase in long-term mortality [6]. Anemia is generally well tolerated by a heart in good health, as it is accompanied by compensatory mechanisms that aid in sustaining oxygen delivery, such as augmented cardiac output. However, the aforementioned mechanisms have the potential to exert deleterious effects in the context of coronary artery disease, thereby potentially precipitating left ventricular dysfunction [7]. The exacerbation of left ventricular dysfunction or ischemia in post-MI patients may be elucidated by the presence of anemia, which could potentially account for the observed increased long-term mortality [8].

Anemia may arise as a consequence of diverse underlying pathologies, each of which possesses the potential to exert an independent influence on overall survival. In order to elucidate this matter, we conducted an analysis on mortality rates specific to the underlying causes. In the present investigation, it was observed that the predominant cause of mortality among the subjects, belonging to both the anemia and non-anemia cohorts, was cardiovascular disease. This outcome was consistent for the duration of 30 days as well as the extended period of 36 months. A notable disparity in cardiovascular mortality rates was observed solely among individuals diagnosed with diabetes who also presented with anemia, in contrast to those without anemia. However, it is worth noting that a significant percentage of individuals within the diabetic cohorts had their cause of demise recorded as 'diabetes,' which may lead to the misclassification of numerous deaths related to cardiac issues as non-cardiac in nature. Significantly, patients presenting with anemia did not manifest noticeably elevated frequencies of non-cardiac etiologies of mortality, including malignancy or hemorrhagic events, thereby underscoring the predominant contribution of cardiovascular pathology to the majority of deceases.

In the course of the investigation, no discernible disparity was observed between the categories in relation to the composite morbidity endpoint within the 30-day timeframe. This lack of distinction may be attributed to the elevated mortality rate observed among patients presenting with both diabetes and anemia. Deceased patients who expired during their hospitalization would not be anticipated to encounter subsequent occurrences. The exclusion of patients who expired within a 30-day timeframe unveiled a discernible pattern indicating an inclination towards heightened rates of readmissions pertaining to unstable angina, recurrent non-fatal MI, and CHF within the cohort characterized by diabetes and anemia. The admissions for CHF and unstable angina (UA) demonstrated an apparent inverse relationship, wherein the category exhibiting a higher frequency of readmissions for CHF compared to unstable angina was solely comprised of individuals with concurrent diagnoses of diabetes and anemia. Silent myocardial ischemia and CHF are acknowledged complications associated with diabetes and anemia, respectively [9].

The present investigation is characterized as a retrospective and observational study, thereby being subject to inherent limitations. The potential impact of unrecorded comorbidities, treatment decisions, and interventions, including blood transfusions, on mortality rates among the four categories cannot be disregarded. However, it is important to note that we have made adjustments for various potential confounding factors, with the exception of transfusions. The identification of readmissions was limited to specific conditions, thereby potentially overlooking additional disparities in outcomes across cohorts. Although the etiology of mortality remained undetermined in 1.7% of the subjects under investigation, it is improbable that this minute proportion exerted any systematic influence on the outcomes. Furthermore, it is noteworthy that certain medical conditions, which are not commonly recognized as immediate precursors to mortality, such as diabetes and hypercholesterolemia, were documented as primary factors contributing to the demise of certain individuals [10]. If anything, it is anticipated that this would fortify the correlation between anemia and cardiovascular disease, given that these conditions are contributory factors to cardiovascular mortality. [11] The study's notable strengths are attributed to its utilization of a substantial and up-to-date population-based cohort, comprehensive clinical data, and the ability to obtain cause-specific mortality data from the provincial Vital Statistics Registry.

Conclusion

In a substantial cohort of consecutive AMI hospitalizations, this study confirms diabetes mellitus as a significant independent risk factor for both short- and long-term mortality. In contrast,

when treated as a binary variable like diabetes, anemia does not independently impact 30-day mortality but is associated with decreased survival over a longer duration. Additionally, there exists a positive correlation between anemia severity and mortality, with higher anemia levels linked to increased mortality up to 36 months. This study is the first to demonstrate that any degree of anemia independently affects extended post-MI mortality. The presence of both diabetes and anemia leads to a notably unfavorable prognosis, with 65% of individuals in this category experiencing mortality within 36 months. Remarkably, cardiovascular disease, rather than conditions like cancer, hemorrhage, or renal failure, is the primary cause of death in anemic patients. Further research is warranted to explore whether addressing anemia can help mitigate long-term mortality in hospitalized AMI patients.

References

1. Sabatine MS, Morrow DA, Giugliano RP, Burton PBJ, Murphy SA, McCabe CH, Gibson CM, Braunwald E: Association of Hemoglobin Levels with Clinical Outcomes in Acute Coronary Syndromes. Circulation. 2005, 111: 204 2-2049.
2. Thomas MC, MacIsaac RJ, Tsalamandris C, Power D, Jerums G: Unrecognized Anemia in Patients with Diabetes: a Cross-sectional Survey. Diabetes Care. 2003; 26(4): 1164-1169.
3. Al Falluji N, Lawrence-Nelson J, Kostis JB, Lacy CR, Ranjan R, Wilson AC: Effect of Anemia on 1-year Mortality in Patients With Myocardial Infarction. Am Heart J. 2002; 144: 636-641.
4. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM: Blood Transfusion in Elderly Patients with Acute Myocardial Infarction. N Engl J Med. 2001, 345(17): 1230-1236. 10.10 56/NEJMoa010615.
5. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Topol EJ, Stamler JS, Califf RM: Relationship of Blood Transfusion and Clinical Outcomes in Patients With Acute Coronary Syndromes. JAMA. 2004; 292: 1555 -1562.
6. Chakdoufi S., Moumen A., & Guerboub A. Dyslipidemia and Diabetic Retinopathy in Moroccans Type 2 Diabetics Patients: A Cross-Sectional Study. Journal of Medical Research and Health Sciences, 2023;6(3): 2471–2479.
7. Bahl VK, Malhotra OP, Kumar D, Agarwal R, Goswami KC, Bajaj R, Shrivastava S: Noninvasive assessment of systolic and diastolic left ventricular function in patients with chronic severe anemia: A combined M-mode, two-dimensional, and Doppler echocardiographic study. Am Heart J. 1992; 124: 1516-1523.
8. Narita M, Kurihara T, Sindoh T, Sawada Y, Honda M: Characteristics of myocardial ischemia in patients with chronic renal failure and its relation to cardiac sympathetic activity. Kaku Igaku. 1999; 36(9): 979-987.
9. Geha AS: Coronary and cardiovascular dynamics and oxygen availability during acute normovolemic anemia. Surgery. 1976; 80: 47-53.
10. Milan Study on Atherosclerosis and Diabetes (MiSAD) Group: Prevalence of Unrecognized Silent Myocardial Ischemia and its Association with Atherosclerotic Risk Factors in Noninsulin-dependent Diabetes Mellitus. Am J Cardiol. 1997; 79(2): 134-139.
11. Mathers CD, Ma Fat D, Inoue M, Rao C, Lopez AD: Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ. 2005; 83(3): 171-177.