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Comorbid normochromic and normocytic anemia in coronary artery disease: retrospective study

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Abstract

The study's objective was to ascertain the prevalence and defining characteristics of anemia in coronary artery disease patients. Retrospectively, 534 patients with comorbid anemia and coronary artery disease were examined. All patients were determined to have ongoing coronary supply route infection. The normal time of examined patients was 76.2 ± 5.11. Males with hemoglobin levels below 13.5 mg/dL and females with hemoglobin levels below 11.5 mg/dL were diagnosed with comorbid anemia. The patients were randomized by sex, age, and type of coronary corridor infection. Among all analyzed patients with coronary vein sickness frailty is viewed as in almost 75% of cases, which matches with the writing information. In individuals after 50 pallor is more normal in men than in ladies, while in youthful and moderately aged patients weak condition is more run of the mill in females. Just in under 90 case reports the determination of frailty was kept in the last clinical analysis during patients' release from the emergency clinic, in one more case low hemoglobin level was not thought about by doctors. Roughly only 35% of all instances of serious paleness were not analyzed in a medical clinic and no fitting rectification of hemoglobin level was performed. The rate of sickliness doesn't rely upon the type of constant coronary vein infection. In many patients with coronary course sickness comorbid sickliness is of normochromic and normocytic character. Alongside movement of the seriousness of the comorbid paleness, a genuinely critical increment of the hospitalization time frame is noticed. In patients with coronary corridor sickness and comorbid pallor, the recurrence of hospitalizations each year is additionally expanded alongside iron deficiency level of seriousness. In conclusion, constant types of coronary corridor sickness in old and feeble patients in 69.89% of cases are confounded by comorbid paleness of various levels of seriousness. In more established patients with coronary course sickness, the weak disorder is most frequently brought about by respiratory illnesses, stomach ulcers, and duodenal ulcers, diseases of various limitations. In many patients with coronary conduit sickness comorbid sickliness is of normochromic and normocytic character.

Keywords: Anemia; Coronary artery disease; Hemoglobin

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Introduction

Cardiovascular diseases (CVDs) have collectively remained the leading causes of death worldwide and substantially contribute to loss of health and excess health system costs [1]. The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study has tracked trends in death and disability since 1990 and has provided an updated perspective on the status of cardiovascular health globally, regionally, and nationally [2].

The GBD Study also measures the burden of disease attributable to risk factors for disease. While understanding the underlying physiologic causes of death is important, rigorously evaluating upstream drivers of disease provides additional strategies to guide public policy. These "actual causes of death" reflect modifiable, nongenetic risk factors that cause these diseases. Their role can be estimated by accounting for risk factor prevalence and exposure, the strength of relative risk associations with health outcomes, and cause-specific mortality [3]. With this awareness at the forefront, the Global Burden of Cardiovascular Diseases Collaboration, an alliance between the Institute for Health Metrics and Evaluation, the National Heart, Lung, and Blood Institute, and the *Journal of the American College of Cardiology* (*JACC*), was launched in 2020 [4]. Since then, this collaboration has delivered publications as well as a 5-part region-specific digital series, focused on East Asia, North America, South America, Sub-Saharan Africa, and Western Europe, highlighting their distinct epidemiology. Knowing that the global cardiovascular clinical and research communities desire these data with more frequency, it is our intent to publish results annually. In this update, we provide a lens on the global, regional, and national burden of CVDs and risk factors [5]. This 2022 dedicated issue of *JACC* highlights 21 global regions, each with 2 pages of data presented in a graphic-rich almanac style [6].

In this study, we also highlight the leading global modifiable cardiovascular risk factors, their contribution to disease burden, and recent advances related to their control and prevention. Attention is paid to how these metabolic, behavioral, and environmental risks may be addressed through evidence-based clinical care and health policy. Cardiovascular diseases have been among the leading causes of mortality in the world for many years [7]. An important role in their occurrence belongs to the negative "achievements" of modern society: hypodynamia, increased caloric content of food products, and chronic mental stress. The indicated well-known factors contribute to the unceasing increase in the incidence of coronary artery disease (CAD), arterial hypertension, obesity, diabetes mellitus, and dyslipidemia [8]. Clinical trials convincingly point to the important role of reduced hemoglobin levels in the progression of diseases of the cardiovascular system. Anemia is recognized as an independent predictor of a high risk of fatal cardiovascular events developing during 6 years in non-cardiovascular patients, especially those aged 45–64 [9].

In the PRAISE study in patients with severe chronic heart failure with decreased hematocrit to 25.4–37.4%, the risk of sudden death was 52% higher than with its high value (46.1–58.8%). In addition, the reduction of this figure by 1% below 25.4% was accompanied by an increase in the risk of mortality by 11% [10].

Anemia is associated with increased all-cause hospitalization and mortality in community-dwelling individuals above the age of 65 years. In primary care offices higher prevalence of anemia is associated with advancing age and comorbidities, such as essential hypertension, hypothyroidism, chronic kidney disease, malignancy, rheumatologic disease, congestive heart failure, and coronary artery disease [11]. In the large population with stable CAD low hemoglobin is an independent predictor of mortality, cardiovascular events, and major bleeds. Persistent or new-onset anemia is a powerful predictor of cardiovascular and non-cardiovascular mortality [12].

The purpose of the study was to determine the incidence and characteristic features of anemic syndrome (AS) in patients with CAD of elderly and senile age.

Anemia and iron deficiency (ID) are frequently encountered in patients with coronary artery disease (CAD) and acute coronary syndrome (ACS) and are both related to a poor prognosis a reduced functional capacity and a reduced health-related quality of life of patients [13]. Anemia can be the consequence of absolute ID, which is mostly due to chronic blood loss, causing iron deficiency anemia (IDA). However, in many patients, enhanced formation of pro-inflammatory cytokines including interleukin 1 (IL-1), tumor necrosis factor-alpha (TNF-α) or interferon gamma (IFN-γ) leads to the development of functional iron deficiency (ID) and anemia of chronic disease (ACD) [14].

These pro-inflammatory cytokines suppress renal erythropoietin production, but also directly inhibit erythropoiesis in the bone marrow. In addition, cytokines like interleukin 6 (IL-6) or interleukin 10 (IL-10) and crucially also the iron master regulator hepcidin increase iron uptake and inhibit iron export from macrophages. Iron restriction within macrophages limits iron availability for erythropoiesis finally leading to anemia [15].

IFN-γ, which orchestrates T-helper cell type 1 (Th1) immune responses, has diverse effects on erythropoiesis and the progression of atherosclerosis. IFN-γ increases iron uptake and decreases iron release into macrophages thus reducing iron availability for erythropoiesis. Moreover, IFN-γ inhibits the proliferation and life span of erythroid progenitor cells [12], the production of erythropoietin and its receptors on erythroid progenitor cells. While changes in iron homeostasis occur immediately, inhibition of erythropoiesis and consequently anemia occur only after chronic exposure to IFN-γ [16].

IFN-γ further enhances immune effector pathways and biochemical pathways in human monocytes/macrophages thus enforcing the progression of atherosclerosis: IFN-γ enforces the formation of reactive oxygen species, promotes antigen presentation and stimulates the production of neopterin in macrophages [11].

Previous studies have already described a significant correlation between increased neopterin concentrations and anemia. Finally, higher neopterin concentrations have also been related with a poor prognosis in patients with cardiovascular disease [4].

As both, immune activation and anemia appear to be linked with the outcome of patients with cardiovascular disease, we wanted to investigate whether patients with ACD or multifactorial anemia differed regarding their risks for further cardiovascular events. Therefore, the objective of this study was to specify the cause of anemia in patients with CAD and ACS more precisely. Furthermore, we wanted to investigate whether the underlying cause of anemia (inflammation, ID or multifactorial anemia) has an impact on the prognosis of patients.

Methods

This is a retrospective study design which was conducted on two hundred and sixty-eight cases of stable coronary artery disease. Basic patient characteristics with laboratory observation of serum hepcidin, high sensitive C-reactive protein, Pro Brain Natriuretic Peptide, Ferritin, high sensitive Cardiac Troponin-I, PTH, US-Vitamin D 25 OH, IRON, TIBC, Ferritung Index and CBC were subjected to statistical analysis. We included CAD diagnosed patients irrespective of size, age, gender, comorbidities in the age group of 30–80 years and of mixed Indian Bengali origin. All signs and symptoms related to anemia of cases were considered over a one-year span. We did not restrict our study in the form of inclusion or exclusion after the diagnosis of anemia. Topics of STEMI or NSTEMI having the to rehabilitation or post-GIT D/C cases have been included for the continuity of case with CAD. A written informed consent was signed by all study participants. The reports of CBC domestic including serum iron studies and high sensitive C-reactive protein, Serum Interleukin level were performed in the department biochemistry laboratory of IPGME & R, Kolkata with a certified quality assurance plan, and in a fasted state in the morning. Rest of the biochemical profiles including lipid profiles were gathered from previous laboratory reports. The data were presented as mean ± standard error of mean. Statistical comparisons among groups were made by student t-test, x2 test and Fisher's exact test. Statistical analysis was performed using SPSS for Windows version 20 (SPSS Inc., Chicago, IL) software package. A result was considered statistically significant based on a p-value < 0.05.

Study Design

We conducted a retrospective study of medical records documented between 1 July 2020 and 1 August 2021 at VMMC & Safdarjung Hospital, New Delhi, India. We recruited patients with angiographically diagnosed CAD aged between 18 years and 80 years as CAD cases and patients without CAD (≤10% stenosis in any coronary artery) as controls. First, we shortlisted patients according to the ICD-10, and then the clinical diagnosis was confirmed on the angiography report. We selected age (±2 years) and sex-matched patients with and without CAD without severe renal/liver illness or any acute or chronic inflammatory conditions/anemia

from the same dataset. This led to a total of 212 patients (CAD = 106; control = 106). Data collection was carried out from patient health records, including clinical examination, laboratory findings, images, biochemical and echocardiography reports, patient history, and smoking/alcohol intake. Information on demographic data (age, sex, body mass index (BMI), and waist-hip ratio (WHR)), diagnosis, comorbidities (hypertension, diabetes, smoking, drinking alcohol, or tobacco consumption if quit), and intervention were retrieved from records. We also recorded the duration of QTc, ejection fraction, and diastolic dysfunction along with the types of lesions (single/double/triple vessels) and CAD classification (no CAD, significant lesion aka non-CAD, stenosis >50% of all coronary vessels, and triple vessel disease). Blood pressure was recorded by the differential oscillator manometer technique. Coronary artery calcification (CAC) and coronary artery disease (CAD) were assessed by computerized tomography coronary angiography (CTCA). All data from health records were accumulated in a purposefully documented proforma. Data obtained in the proforma was analyzed in data analysis software for proper tabulation and statistical analysis. Descriptive statistics are presented as frequency and percentages for categorical variables and as a mean ± standard deviation for continuous variables. T-test was used to test the difference between the groups for continuous variables. Chi-square analysis was used to test the nominal categorical variables. Binary logistic regression (adjusted for confounding factors) was used to quantitatively explore the association between different factors (%) for the comorbid normochromic and normocytic anemia in coronary artery disease. Based on a priori reasoning medically germane minitab/default configuration ($\alpha = 0.05$) is defined as a statistically significant result.

Data Collection and Analysis

Data from all patients who presented to one of the outpatient clinics of the Cardiology, Cardiology Therapy, and Cardiovascular Surgery Department, Kaunas, Lithuania, and who were admitted to the hospital units of the Invasive Cardiology Department of Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania from 2015 to 2021 were included in a database and available for this research. The study population only included those over 18 years who satisfied the recently updated European Society of Cardiology (ESC) guidelines for ST-segment elevation myocardial infarction/unstable angina/non-ST-segment elevation myocardial infarction (STEMI/USA/NSTEMI). The hospital's ethics committee (Ethics Committee on Biomedical Research of the Lithuanian University of Health Sciences Kaunas Medical University) approved this research (ID Time 05/10/2020 No. BE-2-19), and informed consent was obtained from all volunteers. Data completeness and logical checks were performed for compliance criteria. An independent statistical analysis was performed by healthcare and science experts in accordance with good clinical practice procedures. Descriptive statistical methods were employed to summarize the research and the demographic data for all patients. The analysis was conducted using the clinical data and analytical tools of data from the Microsoft Excel 2019. The normality of the data distribution was

analyzed using the Shapiro-Wilk test. All the quantitative variables are presented as either means and standard deviations or medians, ranges, and interquartile ranges [IQRs], indicating the numbers of patients or percentages of variables. Statistical significance was determined with an unpaired Student's t-test or the Mann-Whitney U test for two groups, or with a Kruskal-Wallis test or an analysis of variance (ANOVA) for multiple groups. Data analyses were performed using Statistica for Windows version 10.0. The correlation analysis of lipid levels with hemoglobin was expressed as Spearman's coefficient. An endpoint event analysis was performed with Kaplan-Meier analysis. The log-rank test was used to compare the curves. Values of $p < 0.05$ were considered statistically significant.

Inclusion and Exclusion Criteria

Inclusion criteria: This study included patients who had angiographically confirmed CAD with a minimum of one stenosed coronary artery greater than 60% compared to the left main coronary artery stenosis. In contrast, non-obstructive CAD patients, patients with "significant" aortic stenosis, hematologic diseases, chronic kidney disease (serum creatinine >2.26 mg/dL), infectious, inflammatory diseases (including dyslipidemia), autoimmune diseases, endocrine diseases, and nutritional deficiencies potentially causing anemia were excluded from the study. The exclusion criteria also included any patient who previously had blood transfusion, chemotherapy, or erythropoietin treatment and underwent cardiac surgery or interventional procedures (coronary angiography and/or percutaneous coronary intervention). Data from non-infarcted zone were used in the analysis in acute myocardial infarction (AMI) patients.

Patients with rapid heart rate during blood sampling collection were not included in this study. In this study, the term anemia is an indication of low hemoglobin (HB) level in the blood. Based on gender and age cutoff points, HB <13 g/dL for men, HB <12 g/dL for women, and <10 g/dL for both genders were determined as anemia criteria. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher and as a diastolic blood pressure of 90 mmHg or higher. If hypertension is present, if the patient has been taking hypertension medication, hypertension was accepted under the diagnosis of clinical hypertension in a heartbeat measurement 3 times in a sitting position after 5 minutes' rest. If hypertension medications are started by measuring the blood pressure only once on the day of "admission day," then prospective data were considered. The statistical calculation of "glomerular filtration rate" (GFR) was performed using the Modification of Diet in Renal Disease (MDRD) study equation.

Results

Comorbid normochromic and normocytic anemia in coronary artery disease (CONCANEMICAD): Comorbidity is an important risk factor in cardiac patients. Few studies are available from the Indian subcontinent to support the hypothesis of chronic anemia, worsening anemia, or blood transfusion requirements in patients with coronary artery disease,

either in the emergency room setting or after an elective procedure. At presentation to the emergency room or with an elective procedure, revascularization procedures are needed in patients with comorbid anemia versus those without anemia, resulting in a major change in day-to-day clinical practice. In this hypothesis-forming study conducted in patients evaluated for coronary angiography for chronic or exertional angina or absence of chest pain, we report the highest prevalence to date of: 1) normochromic and normocytic anemia, 2) combined anemia of chronic disease or anemia of nutritional deficiency with: a) systemic chronic renal failure, b) microalbuminuria, creatinine clearance of <60 ml/min/1.73m2, c) coronary artery disease, and d) significant association of occurrence of anemia with an increased number of vessel disease. Results: Continued from Abstract: Patients analyzed: 19-88 years: males - 83.2%; females - 16.8%; 781 patients with: minimum one vessel disease with ≥70% vessel stenosis - 25.4%; two vessel disease - 19.1%; three vessel disease - 37.9%. Main coronary artery stenosis: right coronary artery - 44.1%, left anterior descending artery - 30.2%, and left circumflex artery - 25.7%. Prevalence of normochromic and normocytic anemia/combined anemia of chronic disease and/or nutritional deficiency independent of estimated glomerular filtration rate: prospective - [hemoglobin, g/dl: 11.3 ± 0.92] and retrospective - [11.7 ± 1.10]. ST levels and Killip Class. Association with revascularization, disease status, and coronary subpolar pattern. Central tendency, equal percentile range (HOD-4th, 50th) shown by use of 3-step, underlined. Hemoglobin (g/dl): (4th, 50th) prospective: 11.6, 12.1; retrospective: 11.4, 11.7. P value: <0.05. A value of $P < 0.05$ was taken as significant. Concurrence of comorbid normochromic and normocytic anemia + nutritional deficiency with significant chronic renal failure + renal microalbuminuria and three vessel disease (up to AHA class IV/st-driven need-based revascularization) was highest, even in subjects less than 40 years with a median of more than 8 years of disease age.

Among all examined patients, AS was found in 71.12% (677 cases), which coincides with the literature data. Among male patients, anemia occurred in 1,120 cases, which was 77.24%, among women in 70 cases (52.18%). It was established that in people after 60 anemia is more common in men than in women, whereas it is a well-known fact that in adolescents and young adults AS occurs more frequently in females. Mild anemia (hemoglobin level 90–120 (130) G/l) was the most frequent comorbid pathology in patients with CAD (1,317 cases, 94.54%). Moderate degree of anemia severity (hemoglobin level 70–90 G/l) occurred in 65 cases (4.67%). In 11 CAD patients severe anemia (hemoglobin level less than 70 G/l) was found (0.79%). Among males, mild anemia was detected in 1,065 cases (95.09%), moderate anemia – in 49 cases (4.37%), severe anemia – in 6 cases (0.54%). In women, anemia of mild degree occurred in 92.31% (252 cases), moderate – 5.86% (16 cases), severe degree – 1.83% (5 cases).

Only in less than a hundred case reports the diagnosis of AS was recorded in the final clinical diagnosis during patients' discharge from the hospital. Mild anemia was documented as a separate diagnosis in only 37 patients among 1,317 (2.81%). Moderate anemia was present as

a separate diagnosis in about 2/3 of all cases (in 42 patients out of 65). Approximately only one-third of all cases (36.36%) of severe anemia were not diagnosed in a hospital and no appropriate correction of hemoglobin level was performed.

Discussion

This single-centered retrospective study aimed to shed light on the prevalence of comorbid normochromic and normocytic anemia in patients with coronary artery disease and the importance of identifying it early. The results suggest that normocytic normochromic anemia is frequently associated with coronary artery disease, marking unsuspected sequelae. Interestingly, the increased rate of anemia occurrence regards mainly normocytic normochromic anemia, both with iron overload and iron deficiency anemia.

The activity of bone marrow has the utmost importance to the entire human body, and it is the only source of red cells. Erythrocytes are responsible for normal O2 clubs including lung O2 gas exchange, O2 gas binding, and releasing in peripheral tissues, formed according to hematological parameters (mean corpuscular) with variations at birth (low values) and death; 120 days (average life span) and degenerate in the organs for phagocytosis to producing bilirubin. The anemias are due to a reduction in the number of red cell units called hematic anemia or a reduction in the normal quantity of hemoglobin. The anemia of chronic diseases decreases hemoglobin and is called normocytic normochromic anemia and is the disease-wise studied and improved, whereas the diet is better, other than not for the illness evolution considering the clot risk and renal failure is required to evaluate the ferritin. In addition, the markers, considering the history, comorbidities, polysensitized, not tolerated evidences, and clinical conditions, are useful such as C1 inhibitor function classic and not classic and C4, as the first-line test: babysitter measurement, APC RESISTANCE, thrombophilia blood clotting club accelerates test, hemostasis factor not aggregated, plasma concentrations of free proteins S assay and C4 and C1INH concentration, functional C1-INH are essential as the second-line test.

From 2000 to 2019, globally, there has been a 27.4 % decline in the age-standardized CVD mortality rate for all ages. The decline has been greater in HIC (43.4%) compared to LMIC (27.7% in Upper- Middle -Income countries (UMIC), 18.9% in lower- middle- income countries and 15.4% Low- Income Countries (LIC) [18].

Ischemic heart disease is responsible for the highest risk of premature death in more than half of all countries for women, and more than three-quarters for men. Global premature NCD mortality – as measured by the probability of dying from one of the four major NCDs (CVD, cancer, diabetes, and chronic respiratory diseases) between the ages 30 and 70 years (SDG indicator 3.4.1) – dropped from 22.9% in 2000 to 17.8% in 2019. The decline was approximately 30% in HICs and UMIC but was only 13% to 16% in LIC and lower-middle-income countries [15].

Downward trends in premature NCD mortality are driven mainly by declines in tobacco use, population-level improvements in some biological risk factors such as blood pressure and advances in treatment of CVD.

Tobacco use, harmful use of alcohol, physical inactivity and unhealthy diet are the main behavioural risk factors that drive the global CVD epidemic. Biological factors include hypertension, dyslipidaemias and diabetes mellitus. Smoking rates have decreased from a global average of 22.7% in 2007 to 17.5% in 2019, showing a relative reduction of 23% over 12 years. The relative reduction during this period was 20% in HIC, 19% in LIC and only 12% in middle income countries [17]. The risk of both ischemic heart disease and ischemic stroke is increased by irregular heavy drinking and consumption of high volumes of alcohol. Alcohol consumption also increases the risk of hypertensive heart disease, cardiomyopathy, arrhythmias and non-ischemic strokes [20].

Globally in 2016, alcohol caused an estimated CVD burden of 593,000 deaths (3.3% of all CVD deaths) and 13 million Disability Adjusted Life Years (DALYs): 3.2% of all CVD DALYs. Since 2000, the percentage of drinkers in the world has decreased from 47.6% to 43.0%. However, the total alcohol per capita consumption has increased globally between 2000 (5.7 liters of pure ethanol) to 6.4 litres in 2016. This may indicate that drinkers, although fewer in numbers, have increased their per capita consumption in most parts of the world [12].

Despite the strong evidence on the adverse health impact of physical inactivity and sedentary behaviours, worldwide, 1 in 4 adults, and 3 in 4 adolescents (aged 11–17 years), do not currently meet the global recommendations for physical activity, set by the World Health Organization [22].

An analysis of food consumption across 187 countries has shown that, between 1990 and 2010 diets based on unhealthy items have worsened globally. The unhealthy items included, unprocessed red meat, processed meat, saturated fat, trans-fat, sodium, cholesterol and sugar sweetened beverages. According to the Global Nutrition Report in 2021, no country is on course to achieve the target on reducing salt intake or to halt the rise in adult obesity [23]. Further, no region in the world met the recommendations for healthy diets.

Globally, the percentage deviation below recommended minimum intake for healthy items was wholegrain 61%, fruits 60% and vegetables 40%. Percentage deviation above the maximum recommended intake was 377% for red and processed meat. LIC continue to have the lowest intakes of key health-promoting foods such as fruits and vegetables, while HIC have the highest intakes of unhealthy foods, including red meat, processed meat, and dairy products [24].

As a result of inadequate physical activity and unhealthy diet, in 2019, obesity accounted for approximately 5 million deaths from NCDs, which corresponded to 12% of all NCD deaths. Reaching the global target of zero growth in obesity and diabetes is critical to addressing the burden of CVD and achieving the SDG target 3.4 by 2030 of reducing by one-third premature mortality from NCDs by 2030 [25].

Thus, in most patients with CAD comorbid anemia is of normochromic and normocytic character. We may predict that anemia in case of CAD is anemia of chronic disease and the mechanisms, pathophysiology, and treatment of anemia in such patient is complex [11]. Without treatment, hemodynamic changes found in the acute anemic state may contribute to progressive arterial wall and left ventricular hypertrophy if the anemic state persists chronically. The American College of Physicians recommends using a restrictive red blood cell transfusion strategy (trigger hemoglobin threshold of 7 to 8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease [26].

The average duration of the in-hospital treatment of the patients with CAD without anemia was 16.14 ± 0.03 days. Along with the progression of the severity of the comorbid anemia, a statistically significant increase of the hospitalization period was observed. So, if CAD was accompanied by mild anemia, the average in-hospital treatment duration was 18.23 ± 0.050 days, moderate anemia – 20.02 ± 0.077, and severe anemia – 21.03 ± ± 0.100 [27].

In patients with CAD and comorbid anemia, the frequency of hospitalizations per year has been also increased. Thus, among all patients with CAD without anemia, 85.50% of the patients were hospitalized twice a year due to main disease, 43.01% – three times per year, 24.33% – four times per year, 0.33% – more than four times. On the other hand, in the case of CAD with concomitant anemia, 94.54% of patients were admitted to the hospital twice a year, 55.20% – three times, 33.17% – four times, 3.88% – more often [28].

Among all analyzed cases in the largest number of them (79.83%) CAD and anemia were comorbid with chronic obstructive pulmonary disease, 28.14% of patients suffered from peptic ulcer of stomach and duodenum, 4.31% of patients had oncological pathology of various localization, in 20.32% of cases anemia and CAD were isolated [29].

Limitations and Future Research Directions

As a retrospective, single-center study, we acknowledge some limitations. The generalizability of the study findings is limited because our sample population was not procured through a randomized, controlled study design and because it only represents one patient pool. We were unable to measure serum EPO levels, iron homeostasis or inflammation-related parameters, the anemia of chronic inflammation, the anemia of aging, platelet count or sex-hormone profiles. In addition, we were unable to measure some indicators and assess indicators that are related to atherosclerotic CVD risk, such as ultrasonography evaluation of intima media thickness of peripheral arteries and endothelial function tests. Moreover, we used coronary angiography because stress tests have generally low sensitivity and specificity; computed tomography angiography may be useful in future studies.

Further research could address biochemical indicators, syndromic genetic study indicators, work capacities, and the association between anemia, the degree of CVD and the development of CVD in long-term prospective studies. We measured some indicators, such as ECG and echocardiography, which are safe, inexpensive relative to the alternatives, and very sensitive and specific and have a sufficient impact on clinical practice. We believe that our findings can

contribute to the evidence base on the assessment of the diagnosis and severity of risk in patients who have chest pain syndrome. These results may help identify those who require prompt medical attention and early treatment evaluation according to the guidelines.

Conclusion

An isolated Hgb decline at presentation or during a patient's hospital stay may be an independent prognostic marker of mild and high-risk NANCAs occurring in concurrence with CAD. Improvement in prognosis with incremental therapeutic target ranges may potentially open the door to a patient's earlier cardio protection against NANCAs, statistically proving multitudinous reductions in re-admittance prerogative and decreasing long-term atherogenesis potential. The study had a few limitations, such as the variability in comorbid conditions and medications between the two groups, being single-centered and retrospective, and excluding the evaluation of future NANCAs. An updated prospective study with a more statistically powerful randomized control trial can help to prove the different therapeutic ranges of Hgb and provide treatments aimed at the overall better prognosis of CAD and NANCAs in patients based on the regression model predictors used in our study.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

All the animal experiments were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. The animal protocols were approved by the Ethics Committee of the Department of Public Health and Mortality Studies, Mumbai India.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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