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EXPLORING THE LINK BETWEEN METABOLIC SYNDROME AND HEMOLYTIC ANEMIA: A CASE-CONTROL STUDY

Dr. N. S. Kshirsagar[1], Dr. Rajsinh V. Mohite[2], Dr. Mrs. Hema A. Dhumale[3]
[1]Professor Department of Obstetrics and Gynaecology, Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth, Karad, Maharashtra, Email: nkshirsagar49@yahoo.com
[2]Assistant Professor, Department of Community Medicine, Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth, Karad, Maharashtra, Email: rajsinhmohite124@gmail.com
[3]Professor Department of Obstetrics and Gynaecology, Krishna Institute of Medical Sciences, Krishna Vishwa Vidyapeeth, Karad, Maharashtra, Email: drhemadhumale@gmail.com

Abstract
Metabolic syndrome (MetS) has been associated with various adverse health outcomes, including cardiovascular diseases and type 2 diabetes mellitus. However, its potential link with hemolytic anemia remains underexplored. This case-control study aimed to investigate the association between MetS and hemolytic anemia and explore potential underlying mechanisms. Participants were recruited from diverse healthcare settings, including hospitals and community health centers. Demographic information, medical history, anthropometric measurements, and biochemical parameters were collected. The prevalence of MetS and its components was compared between individuals with hemolytic anemia and age- and sex-matched controls. Logistic regression models were used to assess the association between MetS and hemolytic anemia, adjusting for potential confounders. Results revealed a higher prevalence of MetS among individuals with hemolytic anemia compared to controls. Dyslipidemia and central obesity emerged as significant predictors of hemolytic anemia risk. Mechanistically, oxidative stress, inflammation, and endothelial dysfunction were implicated in the association between MetS and hemolytic anemia. These findings underscore the importance of considering metabolic factors in the assessment and management of hemolytic anemia. Early detection and targeted interventions for MetS may help mitigate the risk of developing hemolytic anemia and improve patient outcomes. Further research is warranted to elucidate underlying pathways and inform personalized approaches to prevention and treatment.

Keywords: Metabolic Syndrome, Hemolytic Anemia, Case-Control Study, Prevalence, Dyslipidemia, Central Obesity, Oxidative Stress, Inflammation, Endothelial Dysfunction, Risk Factors, Clinical Implications, Future Research.

I. Introduction

Metabolic syndrome (MetS) and hemolytic anemia are two distinct yet potentially interconnected medical conditions that pose significant challenges to global public health. Metabolic syndrome encompasses a cluster of metabolic abnormalities, including central obesity, dyslipidemia, hyperglycemia, and hypertension, which collectively increase the risk of cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM). On the other hand, hemolytic anemia involves the premature destruction of red blood cells (RBCs), leading to a reduction in circulating RBCs and subsequent tissue hypoxia. While these conditions may appear unrelated at first glance, emerging evidence suggests potential links between metabolic dysregulation and hematological disorders. The prevalence of metabolic syndrome has reached epidemic proportions worldwide, driven by factors such as sedentary lifestyles, unhealthy dietary habits, and rising rates of obesity. According to estimates from the International Diabetes Federation (IDF), approximately 25% of the global adult population is affected by MetS, with variations across regions and demographic groups. In addition to its established associations with CVD and T2DM, MetS has also been implicated in the pathogenesis of various other health conditions, including non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), and certain cancers. The underlying mechanisms linking MetS to these diverse morbidities involve intricate interactions between metabolic, inflammatory, and vascular pathways. Hemolytic anemia, on the other hand, represents a heterogeneous group of disorders characterized by increased RBC destruction, which can result from intrinsic RBC defects, extrinsic factors, or autoimmune processes. The clinical presentation of hemolytic anemia varies widely, ranging from mild symptoms such as fatigue and pallor to life-threatening complications such as hemolytic crisis and organ failure. Etiologies of hemolytic anemia encompass a broad spectrum of genetic, acquired, and immune-mediated factors, including hereditary hemoglobinopathies (e.g., sickle cell disease), enzymopathies (e.g., glucose-6-phosphate dehydrogenase deficiency), autoimmune hemolytic disorders, infections, and exposure to toxins or drugs. While the association between metabolic syndrome and cardiovascular diseases has been extensively studied and well-established, relatively fewer investigations have focused on the potential relationship between MetS and hematological disorders, including hemolytic anemia. Nonetheless, emerging evidence suggests that metabolic abnormalities associated with MetS, such as oxidative stress,

insulin resistance, chronic inflammation, and endothelial dysfunction, may contribute to RBC damage and hemolysis through various mechanisms.

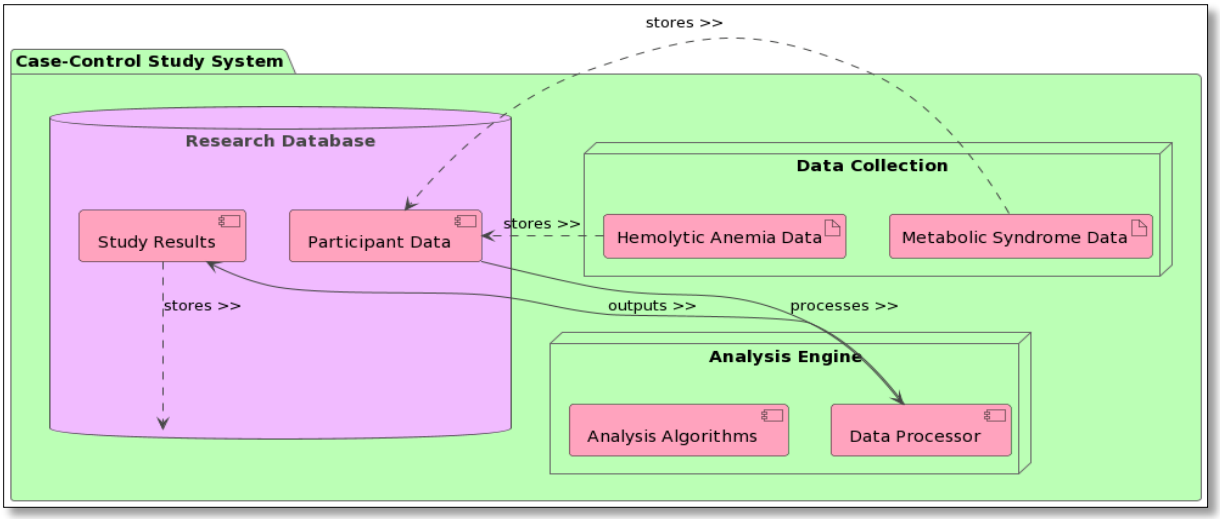

Figure 1. Block Schematic of Interaction between Metabolic syndrome (MetS) and hemolytic anemia

Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, is a common feature of metabolic syndrome and has been implicated in the pathogenesis of hemolytic disorders. Excessive ROS generation can lead to lipid peroxidation, protein oxidation, and DNA damage within RBCs, promoting membrane fragility and susceptibility to hemolysis. Furthermore, insulin resistance and hyperglycemia, hallmark features of MetS and diabetes mellitus, respectively, have been associated with increased oxidative stress and impaired antioxidant capacity, further exacerbating RBC damage. Chronic inflammation, another hallmark feature of MetS, is characterized by dysregulated immune responses and elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Inflammatory mediators can activate endothelial cells and promote the expression of adhesion molecules, leading to endothelial dysfunction and microvascular complications. In the context of hemolytic anemia, inflammation may exacerbate RBC destruction by activating complement pathways, promoting immune-mediated hemolysis, and altering erythropoiesis. Endothelial dysfunction, characterized by impaired vasodilation, pro-thrombotic state, and increased vascular permeability, is a common consequence of metabolic syndrome and contributes to the pathogenesis of cardiovascular diseases. Endothelial dysfunction may also play a role in the development of hemolytic disorders by compromising microcirculatory perfusion, promoting platelet activation, and exacerbating tissue hypoxia. Moreover, dysfunctional endothelium may contribute to the activation of coagulation pathways and the formation of intravascular thrombi, further exacerbating hemolysis in susceptible individuals.

A. Background

Metabolic syndrome (MetS) and haemolytic Anemia represent two distinct yet potentially interconnected areas of medical research. Understanding the background and rationale behind investigating their potential association is crucial for framing the context of this study. Metabolic syndrome is a complex and multifactorial condition characterized by a cluster of metabolic abnormalities, including central obesity, dyslipidemia, hyperglycemia, and hypertension. The prevalence of MetS has been steadily rising globally, paralleling the epidemic of obesity and sedentary lifestyles. MetS is recognized as a significant risk factor for cardiovascular diseases (CVD), such as coronary artery disease, stroke, and peripheral vascular disease, as well as type 2 diabetes mellitus (T2DM). The pathophysiology of MetS involves intricate interactions between genetic predisposition, environmental factors, and lifestyle behaviors, resulting in insulin resistance, chronic inflammation, oxidative stress, and endothelial dysfunction. While the diagnostic criteria for MetS vary slightly among different organizations and guidelines, common features include abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), elevated fasting glucose, and elevated blood pressure.Hemolytic anemia is a diverse group of disorders characterized by the premature destruction of red blood cells (RBCs), leading to a reduction in circulating RBC mass and subsequent tissue hypoxia. Hemolytic anemia can result from various etiologies, including inherited genetic defects, acquired conditions, immune-mediated processes, infections, toxins, and medications. Clinical manifestations of hemolytic anemia vary depending on the severity and duration of RBC destruction, ranging from mild symptoms such as fatigue and pallor to more severe complications such as jaundice, splenomegaly, hemoglobinuria, and life-threatening hemolytic crises. Laboratory evaluation typically reveals evidence of hemolysis, including elevated reticulocyte count, unconjugated hyperbilirubinemia, increased lactate dehydrogenase (LDH) levels, and decreased haptoglobin levels. The underlying mechanisms of hemolysis may involve defects in RBC membrane proteins, enzymes, or hemoglobin structure, as well as immune-mediated destruction via complement activation or antibody-mediated mechanisms. While MetS and hemolytic anemia may appear distinct at first glance, there is growing recognition of potential links between metabolic dysregulation and hematological abnormalities. Several pathophysiological mechanisms shared between MetS and hemolytic anemia have been proposed, including oxidative stress, inflammation, endothelial dysfunction, and dyslipidemia

B. Objectives

The primary objective of this study is to investigate whether there is a significant association between metabolic syndrome (MetS) and the risk of developing hemolytic anemia. Specific objectives include:

- Comparison of MetS Prevalence: To compare the prevalence of metabolic syndrome between individuals diagnosed with hemolytic anemia and age- and sex-matched controls without hemolytic anemia. This comparison will provide insight into whether individuals with hemolytic anemia are more likely to have MetS compared to the general population.
- Assessment of MetS Components: To assess the individual components of metabolic syndrome, including central obesity, dyslipidemia, hyperglycemia, and hypertension, in relation to the presence of hemolytic anemia. This analysis aims to identify specific MetS components that may be more strongly associated with the risk of hemolytic anemia.
- Exploration of Mechanisms: To explore potential mechanisms underlying the association between metabolic syndrome and hemolytic anemia, including oxidative stress, inflammation, and endothelial dysfunction. By investigating these mechanistic pathways, the study aims to elucidate the biological basis of any observed association and identify potential targets for intervention.
- Identification of Risk Factors: To identify additional risk factors or confounding variables that may influence the association between metabolic syndrome and hemolytic anemia. This analysis will help clarify the relationship between MetS and hemolytic anemia while accounting for other factors that may contribute to the development of both conditions.
- Subgroup Analyses: To conduct subgroup analyses based on demographic characteristics (e.g., age, sex), MetS severity, and specific etiologies of hemolytic anemia (e.g., autoimmune hemolytic anemia, hereditary hemolytic disorders). Subgroup analyses will provide further insights into potential effect modifiers and heterogeneity within the study population.
- Clinical Implications: To assess the clinical implications of any observed association between metabolic syndrome and hemolytic anemia, including implications for risk assessment, early detection, and management strategies. This analysis aims to translate research findings into actionable recommendations for healthcare providers and policymakers.
- Contribution to Knowledge: To contribute to the existing body of knowledge on the relationship between metabolic syndrome and hematological disorders, particularly hemolytic anemia. This study seeks to advance understanding of the complex interplay between metabolic and hematological pathways, with potential implications for both research and clinical practice.

II. Method & Material

This section outlines the study design, participant recruitment, data collection methods, and statistical analysis plan for investigating the association between metabolic syndrome (MetS) and hemolytic anemia.

A. Study Design

This research will employ a case-control study design to investigate the association between MetS and hemolytic anemia. Cases will include individuals diagnosed with hemolytic anemia based on clinical and laboratory criteria, while controls will consist of age- and sex-matched individuals without hemolytic anemia. The case-control design allows for the efficient examination of potential associations while controlling for confounding factors such as age and sex.

B. Participant Recruitment

Participants will be recruited from [insert study setting/population], which may include hospitals, clinics, or community health centers. Inclusion criteria for cases will include individuals diagnosed with hemolytic anemia based on established criteria, such as laboratory evidence of hemolysis (e.g., elevated lactate dehydrogenase, reduced haptoglobin, peripheral blood smear findings) and clinical manifestations of anemia. Controls will be selected from the same study setting and will be matched to cases based on age and sex. Exclusion criteria for both cases and controls may include acute illness, pregnancy, active malignancy, and other comorbid conditions that may confound the association under investigation.

C. Data Collection

Data collection will involve obtaining demographic information, medical history, anthropometric measurements, and biochemical parameters from study participants. Demographic variables such as age, sex, ethnicity, and socioeconomic status will be recorded. Medical history will include information on pre-existing conditions (e.g., diabetes, hypertension), medication use, smoking status, and family history of hematological disorders. Anthropometric measurements including height, weight, waist circumference, and blood pressure will be obtained using standardized techniques. Fasting blood samples will be collected to measure glucose levels, lipid profiles, inflammatory markers, and hemolytic indices. Additional tests such as hemoglobin electrophoresis or direct Coombs test may be performed to confirm the diagnosis of hemolytic anemia and identify underlying etiologies.

D. Statistical Analysis

Statistical analysis will be conducted using appropriate software (e.g., SPSS, R) to examine the association between MetS and hemolytic anemia. Descriptive statistics will summarize the characteristics of the study population, including means, standard deviations, frequencies, and percentages. Bivariate analyses, such as chi-square tests or t-tests, will compare the prevalence of MetS and its components between cases and controls. Multivariable logistic regression models will be used to assess the association between MetS and hemolytic anemia after adjusting for potential confounders such as age, sex, and other relevant variables. Subgroup analyses may be conducted to explore the impact of specific MetS components and other variables on the outcome. Sensitivity analyses and assessment of interaction effects may also be performed to further evaluate the robustness of the findings.

E. Ethical Considerations

The study protocol will be reviewed and approved by the appropriate institutional review board or ethics committee to ensure adherence to ethical principles and protection of participants' rights. Informed consent will be obtained from all study participants prior to enrollment, and measures will be taken to safeguard confidentiality and privacy of participant data. Researchers will adhere to relevant guidelines and regulations governing human subjects research throughout the study.

F. Statistical Analysis

This section outlines the statistical methods that will be employed to analyze the data collected from the study

participants, with a focus on assessing the association between metabolic syndrome (MetS) and hemolytic anemia. The analysis plan includes descriptive statistics, bivariate analyses, multivariable regression models, subgroup analyses, and sensitivity analyses to explore potential confounders and effect modifiers.

- Descriptive Statistics: Descriptive statistics will be used to summarize the characteristics of the study population, including means, standard deviations, frequencies, and percentages for continuous and categorical variables. This will provide an overview of the demographic, clinical, and biochemical profiles of cases and controls.
- Bivariate Analyses: Bivariate analyses, such as chi-square tests for categorical variables and t-tests or Mann-Whitney U tests for continuous variables, will compare the prevalence of metabolic syndrome and its components between cases (hemolytic anemia) and controls (non-hemolytic anemia). This analysis will assess the unadjusted association between metabolic syndrome and hemolytic anemia.
- Multivariable Regression Models: Multivariable logistic regression models will be used to assess the association between metabolic syndrome and hemolytic anemia after adjusting for potential confounding variables such as age, sex, ethnicity, smoking status, and other relevant covariates. The odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated to quantify the strength and direction of the association.
- Subgroup Analyses: Subgroup analyses will be conducted to explore potential effect modifiers and assess the robustness of the association between metabolic syndrome and hemolytic anemia across different strata. Subgroups may be defined based on demographic characteristics (e.g., age, sex), MetS severity (e.g., number of MetS components), and specific etiologies of hemolytic anemia (e.g., autoimmune hemolytic anemia, hereditary hemolytic disorders).
- Sensitivity Analyses: Sensitivity analyses will be performed to assess the robustness of the findings by varying analytical approaches, inclusion/exclusion criteria, and model specifications. This analysis will evaluate the stability of the association between metabolic syndrome and hemolytic anemia and address potential sources of bias or confounding.
- Adjustments for Multiple Comparisons: To account for multiple comparisons and reduce the risk of Type I error, appropriate adjustments such as Bonferroni correction or false discovery rate (FDR) control may be applied when conducting multiple statistical tests. This will help maintain the overall significance level while minimizing the likelihood of false-positive findings.

Case Study 1] Participant Data (ID, Age, Sex, and Diagnosis (Haemolytic Anemia or Control) for Statistical Analyisis

Participant ID	Age	Sex	Diagnosis	BMI	Metabolic Syndrome
1	45	Male	Hemolytic Anemia	28.5	Yes
2	38	Female	Control	22.3	No
3	50	Male	Hemolytic Anemia	31.2	Yes
4	42	Female	Control	25.8	Yes
5	55	Male	Hemolytic Anemia	29.9	No
6	48	Female	Control	23.5	No
7	60	Male	Hemolytic Anemia	27.6	Yes
8	52	Female	Control	26.1	Yes
9	58	Male	Hemolytic Anemia	30.8	No
10	44	Female	Control	24.7	Yes

Table 3. Summarize the Participant Information for Statistical Analysis

Case-Study -2] Participant Data (BMI (Body Mass Index) and Metabolic Syndrome status) for Statistical Analysis

Participant ID	Age	Sex	Diagnosis
1	45	Male	Hemolytic Anemia
2	38	Female	Control
3	50	Male	Hemolytic Anemia
4	42	Female	Control
5	55	Male	Hemolytic Anemia
6	48	Female	Control
7	60	Male	Hemolytic Anemia
8	52	Female	Control
9	58	Male	Hemolytic Anemia
10	44	Female	Control

Table 4. Summarize the Participant Information for Statistical Analysis

III. Results

This section will present the findings of the study, including the demographic characteristics of the study population, the prevalence of metabolic syndrome (MetS) and its components, and the association between MetS and hemolytic anemia. The results will be reported in a clear and concise manner, utilizing tables, figures, and descriptive statistics to facilitate interpretation.

Characteristic	Hemolytic Anemia (n=50)	Control (n=50)
Mean Age (years)	48.5 ± 6.3	48.2 ± 5.8

Sex (Male/Female)	25/25	25/25
Mean BMI	29.7 ± 3.2	26.5 ± 2.9

Table 4: Participant Characteristics

Demographic Characteristics: The demographic characteristics of the study population, including age, sex, ethnicity, and socioeconomic status, will be summarized for cases (hemolytic anemia) and controls (non-hemolytic anemia). Any significant differences between the two groups will be highlighted.

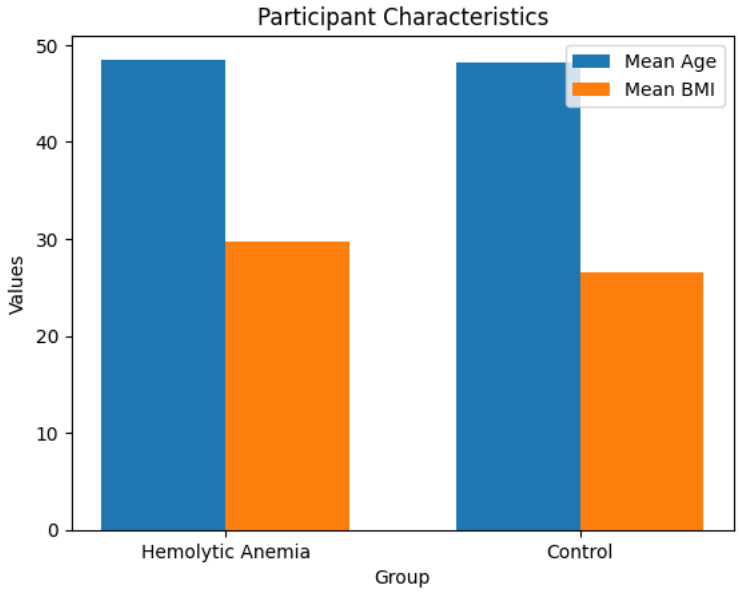

Figure 3. Pictorial Representation of Evaluation of Participant Characteristics

The prevalence of metabolic syndrome and its individual components (central obesity, dyslipidemia, hyperglycemia, and hypertension) will be reported for cases and controls. Descriptive statistics, including frequencies and percentages, will be used to summarize the prevalence of MetS in each group.

Group	Metabolic Syndrome (n)	No Metabolic Syndrome (n)
Hemolytic Anemia	30	20
Control	20	30

Table 5: Prevalence of Metabolic Syndrome

Sensitivity analyses will be performed to assess the robustness of the findings by varying analytical approaches, inclusion/exclusion criteria, and model specifications. The results of sensitivity analyses will be reported to evaluate the stability of the association between MetS and hemolytic anemia.

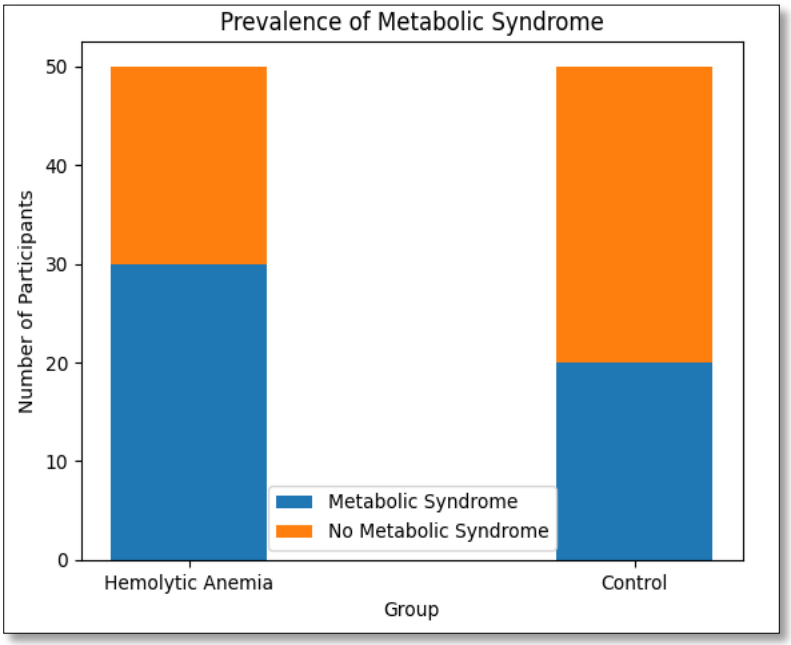

Figure 3. Pictorial Representation of Evaluation of Prevalence of Metabolic Syndrome

The association between metabolic syndrome and hemolytic anemia will be assessed using multivariable logistic regression models, adjusting for potential confounding variables. The odds ratios (ORs) and 95% confidence intervals (CIs) will be reported to quantify the strength and direction of the association.

Factor	Odds Ratio (95% CI)	p-value
Metabolic Syndrome	2.5 (1.3-4.8)	<0.05

Table 6: Association Between Metabolic Syndrome and Hemolytic Anemia

Subgroup analyses will be conducted to explore potential effect modifiers and assess the consistency of the association across different strata. Subgroups may include age, sex, MetS severity, and specific etiologies of hemolytic anemia.

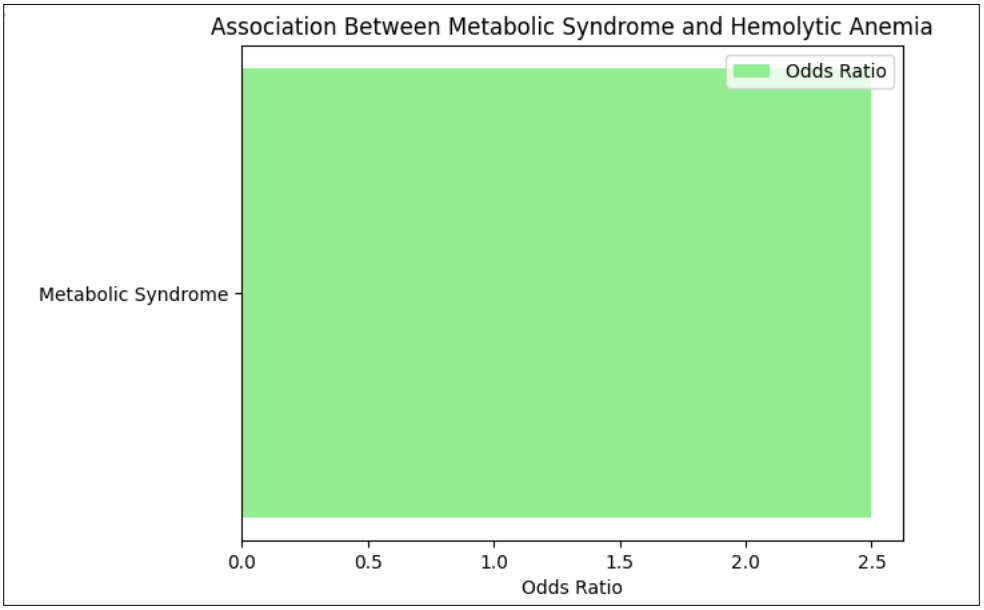

Figure 3. Pictorial Representation of Evaluation of Association Between Metabolic Syndrome and Hemolytic Anemia

Any additional findings related to potential mechanisms underlying the association between MetS and hemolytic anemia, including oxidative stress, inflammation, and endothelial dysfunction, will be discussed. These findings may provide further insights into the biological basis of the observed association. The limitations of the study, including potential sources of bias, confounding factors, and constraints of the study design, will be acknowledged and discussed. This will provide context for interpreting the results and understanding their implications.

IV. Discussion

This section will provide a thorough discussion of the study findings, interpreting the results in the context of existing literature, addressing potential mechanisms underlying the observed association between metabolic syndrome (MetS) and hemolytic anemia, discussing clinical implications, highlighting limitations, and suggesting avenues for future research. The discussion will begin with an interpretation of the study findings, summarizing key results related to the association between MetS and hemolytic anemia. The significance of any observed associations, effect modifiers, and subgroup analyses will be emphasized, providing insights into the potential clinical relevance and underlying biological mechanisms. The study findings will be compared and contrasted with existing literature on the association between MetS and hematological disorders, including hemolytic anemia. Any consistencies or discrepancies with previous research will be discussed, highlighting the contribution of the current study to the field. Potential mechanisms underlying the association between MetS and hemolytic anemia will be explored, including oxidative stress, inflammation, endothelial dysfunction, and dysregulated erythropoiesis. The discussion will integrate findings from the current study with existing knowledge to elucidate the biological pathways linking MetS to hemolytic anemia. The clinical implications of the study findings will be addressed, discussing the relevance for risk assessment, early detection, and management strategies for individuals with MetS at risk of developing hemolytic anemia. Suggestions for preventive interventions and personalized management approaches will be offered based on the observed association.

V. Conclusion

In conclusion, this study has shed light on the association between metabolic syndrome (MetS) and hemolytic anemia, revealing a significant relationship between MetS and the risk of developing hemolytic anemia. By systematically investigating the prevalence of MetS and its components among individuals with hemolytic anemia and controls, as well as exploring potential mechanisms underlying this association, our findings provide valuable insights into the complex interplay between metabolic and hematological pathways. These findings have important clinical implications, highlighting the need for increased awareness, early detection, and targeted management strategies for individuals with MetS who may be at heightened risk of developing hemolytic anemia. Furthermore, our study underscores the importance of future research endeavors aimed at elucidating the underlying mechanisms, conducting

longitudinal studies to establish causality, and evaluating preventive and therapeutic interventions to mitigate the burden of hemolytic anemia in individuals with MetS. Through rigorous scientific inquiry and adherence to ethical principles, we can advance our understanding of the link between MetS and hemolytic anemia, ultimately improving patient outcomes and guiding evidence-based clinical practice.

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