"OVIDIUS" UNIVERSITY OF CONSTANTA
DOCTORAL SCHOOL OF MEDICINE
MEDICINE FIELD

PhD THESIS SUMMARY

Anemia in cardiovascular pathology: transfusion-related, genetic particularities, and association with chronic systemic diseases

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Introduction

KEYWORDS: Cardiovascular pathology, anemia, blood transfusion, associated diseases

INTRODUCTION

One of the topics of great interest in the medical field is represented by blood transfusion in patients with cardiovascular diseases. This category of patients may have certain special requirements, the initiation of blood transfusion involves individual approaches offered based on the clinical variability specific to each case.

The motivation behind this study was the need to determine in detail the role of blood transfusion in the management of patients with cardiovascular diseases, with particular emphasis on indications, benefits, risks, and strategies to optimize transfusion for improved clinical outcomes and to increase the patient's quality of life.

Therefore, this paper presents a systematic review of the red blood cell transfusion process, summarizing the evidence on the impact of the restrictive transfusion protocol and proposals for its reduction, while providing guidance for transfusion management. The guidelines referring to clinical practice for blood transfusions and adjuvant therapies include recommendations to guide physicians in order to improve medical decisions regarding the treatment of certain conditions.

Given these approaches, the aspiration of this paper is to contribute in a major way to the understanding and improvement of transfusion practices, analyzing in depth the effects resulting from transfusion therapy, in order to address certain strategies that may help reduce the incidence of complications related to the procedure.

CURRENT STATE OF KNOWLEDGE

1.Transfusions - general considerations

Blood transfusion is the simple act of transferring blood components of human origin (such as red blood cells, plasma or platelets) from a donor to a recipient, through allogeneic or autologous donation. [1,2] .

Blood transfusion is a common practice in situations where there is blood loss or where a certain pathology requires treatment with blood products or when the oxygen delivery mechanism is compromised and it is necessary to improve the body's ability to ensure the transport of oxygen to organs and tissues.

The "National Nomenclature of Blood Components" includes all the details regarding blood components collected, prepared, preserved, approved, in accordance with the standards imposed, according to Romanian legislation [1] .

2. Basic principles applied in transfusion practice

Blood transfusion may be required for a spectrum of medical conditions. This should require a multidisciplinary approach, and strict adherence to the basic principles of transfusion practice is of great importance. The recommendation for blood transfusion should be in accordance with existing national and international guidelines that specify criteria for the use of blood and blood products. The assessment framework presented in the guidelines helps to identify the real requirements of each patient, while avoiding waste of blood products.

Another principle refers to the management of bleeding, so what matters most is that bleeding is minimized. Therefore, correct diagnoses precede the critical time for intervention and avoid severe complications.

As a general principle, the hemoglobin (Hb) level is essential for assessing a patient's condition, but it is not a primary criterion for making a transfusion decision. It is largely a matter of symptomatic treatment and prevention of complications. In this regard, the patient's signs and symptoms, as well as the general clinical course, should be assessed. The benefits of receiving a transfusion should decisively outweigh the risks.

Monitoring the patient during and after a transfusion is as critical as the entire procedure. A competent healthcare professional should monitor and intervene immediately in the event of an adverse reaction [3] .

3. Blood components

Whole blood is a combination of cellular elements, colloids, and crystalloids. Centrifugation is the process by which these components are prepared and separated based on their differences in density, velocity, and size. Each blood component has a specific indication and to ensure optimal therapeutic efficacy, they must be stored at an appropriate temperature [4] .

These blood components work together to ensure optimal body function by transporting substances, protecting against infection, and maintaining homeostasis.

The blood components are as follows:

- Blood plasma is the most important liquid element of blood, plays an essential role in maintaining homeostasis and supporting the proper functioning of the body. [5] .
- Red blood cell concentrate contains an approximate volume of 210-350 grams of red blood cells and is obtained by centrifugation of whole blood [6] .
- Platelets, also known as thrombocytes, are the cellular fragments responsible for blood clotting. [5]
- Granulocyte concentrate is a blood product derived from whole blood that contains a large number of leukocytes, mainly granulocytes. It is obtained by collecting whole blood followed by separation, after the centrifugation process.

4. Blood groups and the Rh system

4.1. Blood groups

Blood groups are represented by genetically determined antigens present on the surface of red blood cells, of which the most immunogenic are A, B and D (from the ABO and Rh systems), O being classified as a silent gene, and the A and B genes are perceived as dominant genes over O.

The relevance of the ABO system is underlined by the existence of natural anti-A and anti-B antibodies that can cause an extremely serious post-transfusion accident, putting the patient's life at risk.

Approximately 400 different red cell antigens have also been identified, some of the important antigens being those included in the Kidd, Duffy, MNS, and Kell systems. For each of these antigens there are corresponding allu-antibodies, which are present in individuals who do not express them [7] .

4.2. Rh system

The Rh system is one of the most important blood group systems, finding its relevance both in the context of blood transfusions and immune compatibility.

Next in importance to ABO, the Rh system specifies whether red blood cells have the D antigen or not. If a D antigen is present, the person is Rh positive (Rh+) , if not, the person is Rh negative (Rh-). This distinction is also important for avoiding complications related to transfusions and various other medical interventions [8,9] .

Other antigens of the Rh system are C, c, E, e. Immunogenicity is weaker than that of the D antigen, but their determination (determination of the Rh phenotype) is especially important in the case of multiple transfusions and in patients with malignant hematological pathology.

5. Norms, practices and procedures in medical institutions

The norms and practices within medical institutions ensure the standard of care in order to maintain patient safety and facilitate the efficiency of medical services. One aspect to consider that every medical institution must consider is the existence of the forms used for requesting blood products.

Formalizing the request for blood products and clearly documenting the medical need should help avoid their unjustified use. In turn, the request form allows institutions to monitor and control requests, in order to detect misuse and waste of this resource that may be considered limited [10] .

6. Pretransfusion testing

Pretransfusion tests play a crucial role in the stages of the transfusion process, by ensuring the compatibility between the donor's blood and that of the recipient. The tests are designed to prevent adverse reactions, mainly hemolysis that can be determined by the incompatibility of the antigens on the donor's red blood cells and the antibodies present in the recipient's serum [11] .

Pretransfusion compatibility procedures include in vitro tests, such as: saline test, enzyme test and indirect Coombs test (ICT), to which is added the verification of the blood group at the patient's bedside. In certain categories of patients, pretransfusion tests are complemented by the detection of irregular antibodies (DAI) and the direct Coombs test (DCT).

7. Red blood cell concentrate, the central pillar of transfusion therapy

Resuspended red blood cell concentrate (REP) is one of the most used products in transfusion therapy and is indicated in various pathologies characterized by deficiency in the number of red blood cells and implicitly the Hb level, as well as in the proper functioning of red blood cells.

A common indication for erythrocyte transfusion is anemia. Anemia can have multiple causes, including intracorpuscular defects, when the lifespan of erythrocytes is less than 120 days, and extracorpuscular defects when there are alterations in the living environment (plasma, vessels). Anemia can also be caused by infectious agents (malaria, leishmaniasis, toxoplasmosis), drugs (isoniazid, sulfonamides), physical agents (radiation, burns), chemical agents (copper, zinc, lead), traumatic factors. Other causes can be: chronic bleeding, iron deficiency due to insufficient dietary intake or vitamin B12 deficiency, vegetarian diets. In these circumstances, the administration of CER is a life-saving solution. In a unit of erythrocyte concentrate, the Hb concentration is approximately 20g/100 ml and the hematocrit (Hct) is 55-75%.

Anemia, described by the World Health Organization (WHO), refers to a hemoglobin concentration <12 g/dl in females and <13 g/dl in males.

According to WHO, the classification according to the severity of anemia is:

1. Mild anemia: Hb = 10 g/dl - normal;
2. Moderate anemia: Hb = 8 -10 g/dl;
3. Severe anemia: Hb = 6.5 - < 8 g/dl;
4. Life-threatening anemia: Hb < 6.5 g/dl [12] .

8. Thresholds for CER transfusion

A restrictive threshold is considered when the hemoglobin value is below 8 g/dl and a liberal transfusion strategy when the hemoglobin limit is less than 10 g/dl.

These limits do not replace direct patient assessment or the physician's clinical judgment. Patients with cardiac disease represent a special and challenging group, given the lack of data from large or randomized trials.

Improving oxygenation through transfusion must be balanced against the potential risks of worsening heart failure, for example, due to the volume of blood transfused.

The appropriate level of hemoglobin in a given clinical situation is directly proportional to the delivery of oxygen to the tissues to meet metabolic demands. Maintenance of oxygen delivery to the tissues during an acute decrease in Hb concentration depends on two main factors: cardiac output and increased oxygen extraction. These mechanisms require normovolemic conditions by maintaining an adequate circulating blood volume.

9. Transfusion of patients with cardiac pathology

Blood transfusion should be performed with extreme caution in patients with cardiac pathology because it can significantly influence their dynamics and prognosis. These patients often present with anemia, and the most severe cases are represented by congestive heart failure, ischemic heart disease, coronary artery disease, and valvular diseases.

When the level of red blood cells or hemoglobin in the blood decreases, its ability to transport oxygen to tissues and organs is reduced, which can cause hypoxia.

The decision to perform a CER transfusion should be made after careful assessment of the patient's hemodynamic status, the etiology and degree of anemia, the patient's specific physiological adaptations to anemia, and any possible risks associated with transfusion therapy [13,14] .

10. Genetic aspects

10.1. The role of the MTHFR gene mutation in the etiopathogenesis of anemia

Anemia can occur secondary to genetic mutations, approximately 24 mutations of the methylene-tetrahydrofolate reductase (MTHFR) gene have been identified, but two forms: the C677T and A1298C genes, variations of a single nucleotide polymorphism (SNP) are relatively common in many populations worldwide. When there are mutations in the MTHFR gene, the production of this enzyme is inhibited and an excess of homocysteine (Hcy) [15] and an impairment of vitamin metabolism (B9, B12, B6) may occur .

Anemia and homocysteine are interconnected through a variety of physiological and pathological mechanisms, particularly through the metabolism of vitamins B12, B6, and B9 (folate). Folate metabolism plays an essential role in amino acid synthesis, carbon metabolism, and deoxyribonucleic acid (DNA) methylation [16] .

10.2. The role of the MTHFR gene mutation in cardiovascular pathology

Meta-analyses have suggested a link between the MTHFR C677T polymorphism and an increased risk of coronary artery disease [17,18] and elevated plasma homocysteine levels have been observed in hypertensive patients, being positively correlated with blood pressure values and ischemic stroke [19] .

PERSONAL CONTRIBUTION

1. The importance of the thesis

Anemia is one of the most common hematological abnormalities encountered in medical practice, with a significant impact on the prognosis of patients with cardiovascular and chronic systemic diseases. It is not only a biological marker of an underlying pathology, but an active factor in the aggravation of the underlying disease, negatively influencing exercise capacity, tissue oxygenation and long-term survival.

In the context of cardiovascular disease, anemia can accelerate the deterioration of cardiac function by reducing oxygen transport to the myocardium, inducing a hyperdynamic state, and increasing oxygen consumption, leading to hemodynamic decompensation.

Patients with acute heart failure and associated renal failure constitute an extremely vulnerable population, in whom severe anemia frequently requires transfusion of blood products.

Patients with complicated colon cancer and moderate or severe anemia represent another high-risk segment, especially when associated with cardiac pathology. In this category, anemia has a dual impact: on the one hand, it affects tolerance to surgical stress by limiting tissue oxygen reserves, and on the other hand, it increases the risk of perioperative complications, especially in patients with coronary artery disease or pre-existing heart failure.

In parallel with clinical and biological factors, genetic predisposition plays an important role in determining the risk of acute cardiovascular events. MTHFR gene polymorphisms (C677T and A1298C) influence homocysteine metabolism and have been associated with accelerated atherogenesis and thrombosis.

In susceptible populations, including Romania, the identification of these genetic variants may contribute to risk stratification for early-onset myocardial ischemia, facilitating personalized preventive interventions. Thus, the integration of genetic evaluation into clinical practice may open new directions for cardiovascular screening and prevention.

The three studies presented in this thesis approach anemia and its implications from complementary perspectives – acute, perioperative, and genetic – providing a comprehensive picture of how hematological status interacts with cardiovascular pathology and chronic systemic diseases.

In a time when medicine is moving towards personalization and multidisciplinary integration, a deep understanding of these interactions can optimize treatment strategies, reduce complications, and improve survival.

2. General objectives

The paper aims to investigate, from a multidimensional perspective, the role of anemia in cardiovascular pathology, by evaluating the impact of its severity, transfusion strategies, interaction with systemic chronic diseases and genetic predisposition on the prognosis and evolution of patients. The final goal is to formulate conclusions and recommendations that contribute to optimizing clinical management and reducing associated complications.

By correlating the results obtained from the three studies, the paper aims to provide a coherent vision on how anemia, in various clinical contexts and with variable genetic background, influences cardiovascular prognosis. The data obtained can inform the development of clinical decision-making algorithms and personalized treatment and prevention protocols.

3. Motivation for studies

Anemia, regardless of etiology, is recognized as a negative prognostic factor in numerous cardiovascular and chronic systemic diseases. In clinical practice, it is frequently encountered in patients with acute heart failure, neoplastic diseases, renal diseases or metabolic disorders, contributing to the deterioration of the general condition and increased mortality.

However, the way in which anemia severity, transfusion requirements, and genetic factors interact with cardiovascular pathology is insufficiently documented in the Romanian population, and international guidelines still provide variable and sometimes unclear recommendations for the optimal management of these patients.

4. Study 1: The need to optimize transfusion strategies in acute heart failure

4.1. Introduction

Acute heart failure is a major cause of morbidity and mortality worldwide, with a significant impact on health systems. In the acute setting, the increased myocardial oxygen demand, associated with reduced functional reserves, makes any deficit in oxygen transport capacity have important clinical consequences. In cardiology practice, transfusion thresholds and patient selection criteria remain inconsistent, and decisions are often based on clinician experience and emergency situations, rather than on robust evidence adapted to the local context.

4.2. Material and method

The present study is a retrospective observational study, conducted within the Cardiology Department of the County Emergency Clinical Hospital in Constanța, Romania. The analyzed period was between January 1, 2021 and December 31, 2021, on a group of 270 patients, hospitalized for acute congestive heart failure, with variable degrees of renal failure, who required blood product transfusion to correct severe anemia.

The relationship between anemia severity, transfusion requirement, and clinical outcome of hospitalized patients with acute heart failure, with or without chronic kidney disease, is analyzed to identify prognostic factors and optimize transfusion strategies.

4.3. Results

In the analyzed group, consisting of 270 patients with acute heart failure and anemia, the monthly distribution of hospitalizations showed values ranging from 5.18% (14 cases, June) to 10.37% (28 cases, February and September). (Table 2) The highest percentages were recorded in February and September (28 patients each, representing 10.37% of the total), followed by November (10.00%, 27 cases) and January (9.26%, 25 cases). The lowest values were recorded in the summer period - June (5.18%, 14 cases) and July (5.55%, 15 cases).

The results indicate a high prevalence of elderly patients, especially in the 60–70 and ≥80 years groups, which is consistent with the epidemiological profile of acute heart failure and associated anemia. The clinical interpretation of these data suggests that the severity of anemia varies significantly between diagnostic categories, being more pronounced in arrhythmias and STEMI, which may reflect both distinct pathophysiological mechanisms and different transfusion strategies.

In the group without chronic kidney disease (CKD), patients over 65 years of age were more frequent in the category of those who received 1–2 units (65%) than in the category with 3–4 units (43%), a statistically significant difference ($p = 0.04$). Regarding gender, only 30% of women received 1–2 units, compared to 71% in the category with 3–4 units ($p = 0.001$).

Regarding the severity of heart failure, patients with NYHA III and IV were more numerous in the 3–4 unit category (64% and 58%, respectively), compared with those with 1–2 units (59% in both classes), the differences being at the border of statistical significance ($p = 0.02$ and $p = 0.05$). LVEF was similar between subgroups (36% for 1–2 units and 31% for 3–4 units, $p = 0.12$), without significant differences.

4.4. Conclusions

1. Patients with chronic kidney disease had significantly higher rates of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA) compared with those without CKD, with a relative risk of up to nearly 4-fold higher for NSTEMI/UA.
2. The incidence of arrhythmias was higher in patients with CKD than in those without CKD, with a risk more than twofold, suggesting a common pathophysiological mechanism between renal dysfunction and cardiac electrical instability.
3. Metabolic cardiomyopathy did not show a significant association with CKD, indicating that the CKD–cardiac dysfunction relationship may be influenced more by ischemic and arrhythmic pathology than by chronic metabolic mechanisms.
4. Biological parameters and ventricular function improve significantly at discharge in CRS1, with increased hemoglobin, improved left ventricular ejection fraction (LVEF) and reduced creatinine, highlighting the positive effect of early treatment optimization.
5. Hemoglobin is a superior predictor of in-hospital mortality than eGFR.
6. Severe hemoglobin decrease on admission correlates with increased transfusion requirements, independent of CKD status, emphasizing the importance of rapid identification and correction of anemia.
7. Patients with cardiorenal syndrome had the highest in-hospital mortality (22.5%), exceeding both the CKD and non-CKD groups, which confirms the reserved prognosis of cardiorenal syndrome type 1.
8. The high mortality in patients with LVEF >50% in CRS1 suggests that extracardiac factors contribute significantly to death, exceeding the impact of ventricular function.
9. The significant differences between admission and discharge values for clinicobiological parameters in CRS1 patients confirm that the response to treatment can be rapid and measurable, with prognostic potential.
10. Integration of cardiac and renal assessment is essential in the management of critically ill patients, and the therapeutic approach must include not only optimizing renal function, but also correcting anemia and hemodynamic stabilization.

5. Study 2: management of perioperative anemia in patients with colon cancer and cardiac comorbidity

5.1. Introduction

Oncology patients with associated cardiac pathology present a dual challenge: high perioperative risk and vulnerability to postoperative complications. In the absence of specific data on the interaction between tumor anemia, emergency transfusion requirements, and cardiac status, the surgeon and anesthesiologist are faced with difficult decisions in a limited time. The current study aims to describe the biological profile and postoperative evolution according to the severity of anemia and the presence of cardiac comorbidity, providing a useful database for perioperative treatment adjustment and complication prevention.

The study aims to comparatively analyze patients with complicated colon cancer and moderate or severe anemia, with and without associated cardiac pathology, highlighting the clinico-biological particularities and the transfusion impact on the perioperative evolution. The results may contribute to the optimization of transfusion protocols and management strategies in this category of patients with high vulnerability.

5.2. Material and method

The study was designed as a retrospective case-control analysis, conducted between January 2020 and December 2024, within the Department of General Surgery of the Emergency County Clinical Hospital of Constanța, Romania. Consecutive adult patients diagnosed with complicated colon cancer, accompanied by moderate or severe anemia, who required blood transfusion in the perioperative period were included.

5.3. Results

The distribution of patients in the study was initially carried out according to the severity of anemia, with them being divided into two categories: patients with moderate anemia and patients with severe anemia.

In the moderate anemia group (n = 124), the age variation was significant (SD = 9.98 years), with a range between 35 and 85 years, with the majority of patients being between 58 and 71 years (25th–75th percentiles).

In the severe anemia group (n = 29), the age variation was greater (SD = 11.24 years), with a narrower range (42–81 years), but with a more uniform distribution between percentiles. The ACCI score dispersion (SD = 1.33) was similar to that in group M. The estimated 10-year survival showed an equally high variability (SD = 29.21%), but with lower median values, confirming the unfavorable prognosis.

Comparative analysis of the clinical-biological and postoperative characteristics of the patients included in the study, stratified according to the presence or absence of cardiac pathology, reveals statistically significant differences for several variables with potential prognostic impact.

BMI did not differ significantly between groups, being on average 26.7±3.88 kg/m² in patients without cardiac pathology and 26.1±3.94 kg/m² in those with cardiac involvement (p=0.190), which suggests that weight status did not influence their distribution.

Regarding the severity of anemia, patients with cardiac pathology presented a slightly higher proportion of cases with severe anemia (20%) compared to those without cardiac involvement (18.5%), a statistically significant difference (p=0.017). This observation has clinical relevance, as severe anemia in cardiac patients may worsen perioperative myocardial ischemia by decreasing oxygen transport capacity.

5.4. Conclusions

1. The presence of preexisting cardiac pathology significantly amplified the perioperative risk in patients with colon cancer and anemia, with them presenting higher rates of postoperative complications and reduced overall survival compared to patients without cardiovascular comorbidities.
2. Tumor anemia was a major vulnerability factor, but its clinical impact was much more pronounced in patients with heart disease, where the imbalance of tissue oxygenation contributed to hemodynamic instability and the occurrence of severe complications.

3. The need for transfusion was higher in the group with associated heart disease, which reflects both the severity of anemia and the reduced tolerance of these patients to oxygen deficiency, but at the same time it correlated with a higher rate of postoperative adverse events.
4. Intraoperative blood loss had a disproportionate clinical impact on patients with heart disease, in whom even moderate volumes of bleeding led to cardiovascular decompensation and higher transfusion requirements.
5. Major postoperative complications (Clavien-Dindo ≥ III) were more common in patients with heart disease, indicating that low physiological reserve and poor cardiovascular status amplify the effects of anemia and surgical stress.
6. Long-term perioperative mortality was significantly higher in the anemia–cardiopathy group, confirming that this combination represents a dual independent risk factor.
7. Advanced age was an additional predictive factor of cardiovascular risk in the context of anemia and colon cancer, emphasizing the impact of comorbidities on prognosis.
8. Diabetes mellitus enhanced cardiovascular risk and contributed to a more unfavorable outcome in patients with heart disease, suggesting that metabolic syndrome and tumor anemia have a negative synergistic effect.
9. Smoking, although not directly associated with the incidence of heart disease in the cohort, reduced survival particularly in patients with heart disease, reinforcing the idea of a cumulative effect of risk factors.
10. The integrated assessment of perioperative risk must take into account not only the oncological status and the degree of anemia, but also the existence of associated heart disease, as this radically modifies the body's tolerance to hypoxia and surgical aggression, being decisive for the prognosis.

6. Study 3: Evaluation of genetic predisposition to myocardial ischemia through mthfr polymorphisms

6.1. Introduction

Investigating the interaction between genetic determinism (MTHFR C677T/A1298C) and clinical factors such as anemia and transfusion in the context of a first myocardial ischemic episode represents an opportunity to understand the complex substrate of the disease.

This integrative approach has the potential to define subgroups of high-risk patients, optimize transfusion treatment strategies, and support the development of personalized medicine in ischemic heart disease. Primary objective was investigating the relationship between the MTHFR C677T and A1298C polymorphisms and the risk of a first episode of myocardial ischemia, by comparing the distribution of genotypes between patients with myocardial ischemia and healthy subjects

6.2. Material and method

The study was designed as a case-control study, conducted over a two-year period, between February 2023 and February 2025, within the Cardiology Clinic of the Constanta County Emergency Hospital. The case group included 69 adult patients diagnosed with a first episode of myocardial ischemia or myocardial infarction (MI). For comparability, a control group of 55 healthy subjects, recruited from the same geographical area, with no history of major cardiovascular or chronic diseases, was established.

Genotyping for the MTHFR C677T (rs1801133) and A1298C (rs1801131) gene polymorphisms was performed by a modern real-time PCR (RT-PCR) method, using the Bosphore® MTHFR 677-1298 Detection Kit v2 (Anatolia Geneworks, Turkey).

6.3 Results

The representation of the study results was performed on the two comparative groups: patients with myocardial ischemia and patients from the control group, in the form of representative tables and graphs.

The comparative analysis of the two groups highlights significant differences both in terms of demographic and behavioral distribution, as well as relevant clinical parameters.

The most notable and statistically significant differences were evident in hemodynamic parameters. Systolic blood pressure values were significantly higher in patients with myocardial ischemia (139.41 ± 34.72 mmHg) compared to the control group (119.65 ± 2.11 mmHg), p = 0.044. This aspect confirms the role of arterial hypertension as a determining factor in the onset and aggravation of ischemic processes, being one of the strongest recognized risk factors for coronary heart disease.

group is characterized by a considerably higher proportion in the ischemic group (43.5%, n = 30) compared to the control group (27.3%, n = 15), indicating that this age decade represents a critical point of vulnerability for the occurrence of myocardial ischemia. Patients with ischemia were also frequently encountered in the 50–59 year age group (18.8% vs. 21.8%) and 70–79 year age group (18.8% vs. 25.5%), but the differences were not sufficiently pronounced to reach statistical significance.

For the C677T polymorphism, patients with myocardial ischemia presented an increased frequency of the mutant T allele (80.4%) compared to the control group, where it was only 16.4%, the difference being particularly suggestive of an association between this genetic variant and predisposition to ischemia. At the same time, the wild-type C allele was significantly more frequent in the control group (83.6%) than in ischemic patients (19.6%).

This distribution indicates a genetic imbalance and suggests a possible role of the C677T mutation as a predisposing factor for the occurrence of myocardial ischemia.

Regarding the A1298C polymorphism, ischemic patients presented a higher frequency of the C allele (71.7%) compared to the control group, where it was present in only 11.8% of the subjects. Correspondingly, the protective A allele was significantly more prevalent in the control group (88.2%) than in the patients (28.3%). Again, the Hardy–Weinberg analysis showed a significant deviation in the control group (p = 0.001).

From a clinical point of view, these data support the idea that both polymorphisms of the MTHFR gene – C677T and A1298C – are involved in the susceptibility to myocardial ischemia. The increased frequency of mutant alleles in patients suggests a major contribution of these variants to the disruption of folate metabolism and homocysteine accumulation, a recognized pathogenic mechanism in the development of atherosclerosis and ischemic events.

6.4. Conclusions

1. The ACCI score is the best clinical predictor of myocardial ischemia – with an AUC of 0.88, the age-adjusted comorbidity score has significantly higher discriminative value than age or BMI alone, confirming its utility in prognostic assessment.
2. The age of the patients does not have sufficient predictive value for ischemia, the AUC being only 0.37, which suggests that the ischemic risk depends more on the comorbid context than on the biological chronology.
3. The C677T genotype directly influences 10-year survival in the presence of ischemia – TT homozygous patients show a marked decrease in survival (<50%), compared to CT heterozygous carriers, who maintain high survival (>80%).
4. The A1298C genotype has a differential effect on ischemic risk – AA homozygotes present ischemia only in the context of a high ACCI score (≥4–5), suggesting a protective role, while CC carriers develop ischemia even at moderate scores.
5. The distribution of ischemia by genotypes confirms the increased predisposition for TT (C677T) and CC (A1298C) – ischemia is significantly more common in these patients, indicating that these genetic variants are independent risk factors.
6. Heterozygotes may have a favorable profile – CT (C677T) and AC (A1298C) patients had better survival and the phenomenon of ischemia occurred less frequently, which may suggest an intermediate or even protective effect compared to homozygotes.
7. The interaction between genotype and ACCI score defines different risk thresholds – in the AA genotype ischemia occurs only at increased ACCI, while in CC ischemia occurs earlier, which demonstrates the usefulness of genetic integration in clinical prediction models.
8. Overall survival at 10 years is significantly diminished by myocardial ischemia, regardless of genotype, but the impact is more severe in carriers of risk variants (TT and CC).
9. The association of genetic markers with clinical parameters allows for a finer stratification of ischemic risk – which supports the concept of personalized medicine, in which patients with a genetic risk profile should be monitored more closely even at intermediate clinical scores.

10. The results confirm the role of MTHFR polymorphisms as prognostic markers and not just biochemical ones, influencing not only homocysteine levels but also the relationship between comorbidities, ischemia and long-term survival.

7. General conclusions

1. Anemia in acute heart failure is independently associated with unfavorable clinical outcome, frequently requiring transfusion, and the severity of anemia correlates with renal dysfunction (CKD/AKI) and worsening functional status (NYHA), creating a cardioreno-hematological vicious circle.
2. Transfusion strategies in cardiac patients must be individualized: restrictive thresholds are generally safe, but become suboptimal in severe anemia with tissue hypoxia or hemodynamic instability; extended ABO/Rh compatibility and alloantibody screening reduce the risk of immunization and late transfusion events.
3. The effectiveness of CER transfusion depends on the concomitant correction of iron deficiency (TSAT/ferritin) and control of volume overload; without substrate management (iron deficiency, inflammation, renal failure), the hematological response is transient and the cardiac prognosis does not improve sustainably.
4. In emergency colon cancer surgery, moderate-severe anemia amplifies perioperative risk, and the coexistence of cardiac pathology increases the likelihood of major complications (Clavien-Dindo ≥ III), high transfusion consumption and mortality; preoperative hemoglobin optimization and "patient blood management" are essential.
5. Cardiopathy associated with cancer and anemia requires a fine balance between transfusion requirements (for oxygen delivery) and the risk of volume overload/ischemia; multimodal protocols (iv iron, selective EPO, meticulous hemostasis, blood salvage) reduce exposure to blood products and subsequent complications.
6. MTHFR polymorphisms (C677T and A1298C) are clinically relevant: the risk genotypes (TT for C677T, respectively CC for A1298C) are associated with an increased probability of a first episode of myocardial ischemia, and their effect is more pronounced at ages ≥50 years.

7. Gene–environment interaction is determinant: the impact of MTHFR genotypes on ischemia and survival is amplified by comorbid burden (ACCI), nutritional status (BMI/obesity) and lifestyle factors (smoking), supporting the need for an integrated assessment.
8. ACCI outperforms isolated markers (e.g. age or BMI) in discriminating ischemic risk and predicting long-term prognosis; inclusion of comorbidity scores in transfusion decision algorithms and perioperative risk stratification improves clinical accuracy.
9. Long-term survival is cumulatively affected by anemia, ischemia, and comorbidities; isolated correction of hemoglobin, without addressing comorbidities and iron deficiency, does not consistently translate into survival benefits.
10. Modern management of anemia in cardiovascular pathology must be personalized and staged: rigorous etiological diagnosis (iron, inflammation, B12/folate, hemolysis), preoperative/prehospitalization optimization, targeted transfusion, alloimmunization prophylaxis, and post-transfusion monitoring oriented on clinical outcomes.
11. The integration of genetic profiling (MTHFR) with hematological biomarkers and clinical scores allows the definition of high-risk subgroups, in which secondary prevention (aggressive risk factor control, folate/B complex supplementation when indicated, homocysteine monitoring) can favorably modify the natural history of the disease.
12. The thesis supports a model of personalized cardio-hematological medicine, in which transfusion decisions, perioperative oncological risk assessment and prevention of ischemic events are guided by a synthesis between clinical data, genetic profile and comorbidities, with the potential to reduce complications, blood consumption and mortality.

8. Originality of the thesis

1. Multidimensional integration of anemia in cardiovascular pathology – the thesis does not address anemia only as an isolated hematological phenomenon, but systematically correlates it with acute heart failure, emergency oncological surgery and first-episode

myocardial ischemia, which represents a complex perspective, rarely encountered in the specialized literature.

2. Comparative evaluation of transfusion strategies in cardiac patients with anemia – study 1 provided original data on the impact of anemia severity and renal comorbidities on transfusion requirements and clinical prognosis, outlining personalized indications for CER transfusion.
3. Correlating for the first time, in a national cohort, anemia in complicated colon cancer with associated cardiac pathology – study 2 highlighted how the presence of cardiopathy modifies the perioperative risk profile and transfusion requirements, contributing to a better definition of the concept of patient blood management in emergency oncological surgery.
4. Introduction of the ACCI score in ischemic risk stratification in MTHFR patients – study 3 demonstrated that the association between MTHFR polymorphisms and myocardial ischemia is significantly influenced by the occurrence of comorbidities, an original approach that integrates genetic testing and validated clinical scores.
5. Demonstration of the differential impact of MTHFR genotypes (C677T and A1298C) on myocardial ischemia in age and sex subgroups – stratified analysis revealed clinical particularities that can inform secondary prevention decisions and specific therapeutic guidance.
6. Correlating transfusion with genetic profile – by integrating genetic data with transfusion and clinical status, the thesis makes a unique contribution to understanding how genetic predisposition, anemia, and therapeutic interventions interrelate in cardiovascular diseases.
7. Proposing a translational cardio-hematological model – by combining laboratory data (hemoglobin, iron, homocysteine), genetic factors (MTHFR), clinical scores (NYHA, ACCI, Clavien-Dindo) and transfusion results, the thesis advances an original framework of personalized medicine applied in cardiovascular and oncological practice.
8. The use of complex statistical analyses (ROC, multivariate regressions, subgroup stratifications) to highlight clinical-genetic correlations, which adds soundness and methodological innovation to the work.

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