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Cardiovascular risk in elderly Egyptians with myelodysplastic syndromes

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Abstract

Background Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell-derived disorders manifested by cytopenias peripherally. MDS initiates an inflammatory process which lead to atherosclerosis. Patients with MDS have 1.5-fold higher risks of cardiovascular risks.

Objective Evaluation of cardiovascular risk and unraveling the possible correlation of carotid intima media thickness (CIMT) with clinical, hematologic, and laboratory variables in elderly patients with MDS.

Methods We conducted a case–control research on 168 participants to elicit the serum level of homocysteine, serum high-sensitive C-reactive protein (Hs-CRP), and CIMT in relation to cardiovascular risk, 84 of whom had MDS diagnoses. From March 2021 to the end of May 2023, we chose them among the inpatients and outpatients of the Menoufia University Hospitals' Clinical Hematology Division. We contrasted the chosen MDS patients with 84 healthy individuals as controls.

Results Right and left CIMT were significantly higher in MDS patients than controls as well as for lipid profile, blood pressure, blood sugar, and Hs-CRP. Homocysteine was higher in MDS patients but of no statistical significance.

Conclusion As CIMT and C-reactive protein level were significantly higher in studied patients, we may consider MDS group of patients to have higher risk for cardiovascular disease than normal people.

Keywords Myelodysplastic syndromes (MDS), Carotid intima-media thickness (CIMT), CRP, Homocysteine, Cardiovascular risk

Introduction

The risk factors for cardiovascular disease (CVD) and cancer are increasingly similar, and many people who have been diagnosed with cancer also have CVD risk factors such as age, hypertension, tobacco use, and diabetes [1]. Ineffective hemopoiesis, cytopenias, and an increased susceptibility to acute myeloid leukemia are some of the features of myelodysplastic syndromes (MDS), which are clonal stem cell diseases of the bone marrow [2].

MDS has a built-in propensity to lead to the emergence of CVD. In 2017, Jaiswal and colleagues reported that those with clonal hematopoiesis of indeterminate potential (CHIP), a precursor to MDS, had a risk of coronary heart disease that was almost two times as high [3]. One study found that the burden of cardiovascular deaths was also significantly higher in lower risk MDS, as compared with higher risk disease [4], whereas no study has investigated the effect of MDS-specific treatments on CVD morbidity and mortality [5].

Myeloid-derived suppressor cells (MDSCs) are the primary cells that appear to be engaged in operationalizing

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the inflammatory response. Researchers discovered that these cells are noticeably more numerous in MDS patients' bone marrow, and they seem to have the function of inhibiting the production of blood. They are genetically distinct or separate from the MDS clone and will inhibit and kill nearby bone marrow cells. This data raises the possibility that MDSCs drove the formation of the MDS clone and may have predated it [6].

Aim of the study

Evaluation of cardiovascular risk and unraveling the possible correlation of CIMT with clinical, hematologic, and laboratory variables in elderly patients with MDS.

Methods and approaches

On one-hundred and sixty-eight (168) participants, we conducted a case control. We chose 84 patients with myelodysplastic syndromes (MDS) from the outpatients and inpatients of the Menoufia University Hospitals' Clinical Hematology Division between the beginning March 2021 to the end of May 2023. We contrasted the chosen MDS patients with 84 healthy volunteers who were matched for age and gender.

Patients are previously diagnosed in accordance with the World Health Organization 2016 (WHO) criteria for classification and diagnosis of myeloid neoplasm and acute myeloid leukemia (AML) and were under treatment. For a financial shortage, we had not do a cytogenetic studies so we did not have an IPSS score.

Ethics-related matters

All patients and normal controls were consented according to IRB-approved protocol before being subjected to inspection and inquiry. Every procedure was carried out in compliance with the institutional research committee's ethical standards. The Faculty of Medicine's Ethics Committee gave the study the approval (2021).

Inclusion standards

Adult with MDS over the age of 55, patients < 55 years old, those with suspected secondary myelodysplasia, and those with known chronic liver disease (CLD), chronic kidney disease (CKD), chronic inflammatory or autoimmune disease are excluded, and also patients with established history of having diabetes mellitus.

Methods

- Comprehensive history taking including age, sex, smoking, family history of premature coronary artery disease (CAD), complete physical examination (cardiac, chest, abdominal, and neurological examination), blood pressure with special emphasis on height (m^2) and weight (kg), and body math index BMI (kg/m^2).
- Clinical examination: A general check-up that looks at things like consciousness, body mass index, skin tone, indications of anemia, indicators of a predisposition to bleed such petechial hemorrhage and purpura, and indications of neutropenia as infection and fever, adding physical exam (cardiac check for heart failure, chest check for diseases and infections, neurological testing for stroke history, lower limb deep venous thrombosis (DVT) testing, abdominal hepatosplenomegaly testing, prior surgery)
- Standard investigation: Lipid profile from laboratory blood film-fasting sugar levels-HbA1c-HOMA-IR, a homeostatic model assessment for insulin resistance, homocysteine, high-sensitive CRP (normal up to 10 mg/L), and carotid intima-media thickness CIMT (cutoff level Rt is 0.8 and Lt 0.78 mm)

Analytical statistics

An IBM personal computer running the Statistical Package of Social Science (SPSS) version 22 (SPSS, Inc., Chicago, IL, USA) was used for data collection, tabulation, and statistical analysis. There were two distinct statistical analyses: Examples of descriptive statistics include percentages, means, and standard deviations. Chi-square test (χ^2) was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (standard deviation) and range.

Independent *T*-test was used to calculate difference between quantitative variables in two groups for parametric variables. Spearman's correlation coefficient was used for correlating variables. Significant was defined as a P-value ≤ 0.05.

Result

From 84 studied MDS cases, we demonstrated that 65.5% of them were females with mean age 65.82 ± 4.45 years and mean BMI of 26.31 ± 2.56 kg/m^2. A total of 25% of the patients were smokers, and 15.5% were hypertensive, while 7.1% had positive family history of premature coronary artery disease. The mean systolic blood pressure SBP was 132.12 ± 16.44 mmHg, and the mean diastolic blood pressure DBP was 80.88 ± 10.66 mmHg.

Moreover, 57.1% of the patients were low socioeconomic status, 36.9% were intermediate socioeconomic status, and 6% were high socioeconomic status based on household income and subjective perception. Regarding mean and standard deviation of some laboratory results, cholesterol level was 166.83 ± 36.1 mg/dL, triglycerides TG were 108.67 ± 68.85 mg/dL, high-density lipoprotein HDL was 49.37 ± 14.34 mg/dL, low-density lipoprotein

LDL was 100.82 ± 34.35 mg/dL, fasting blood sugar FBS was 101.8 ± 53.04 mg/dL, HbA1c 5.76 ± 1.03%, homeostatic model assessment for insulin resistance (HOMA) IR 2.07 ± 1.41, Hs-CRP (mg/L) was 6.63 ± 2.46, homocysteine 3.91 ± 4.11, right CIMT 0.851 ± 0.291 mm, and left CIMT 0.899 ± 0.343 mm (Table 1).

Comparing cases to 84 subjects (of same age and sex), as controls, the demographic, clinical, and laboratory data revealed that there was significant difference between cases and controls regarding levels of total cholesterol, LDL, triglycerides, FBS, 2 h-PPG, SBP, and CRP. However, there was a difference between the groups regarding homocysteine but of no significance (Table 2).

Right and left CIMT (mm) were significantly higher among cases compared to controls (P-value < 0.001) (Table 3).

There was significant positive correlation between CIMT and the following parameters: cholesterol level, TG level, HOMA-IR, Hs-CRP, and the white blood cells count (Table 4). CIMT and Hs-CRP had a strong positive connection ($p = 0.007$) (Fig. 1).

Table 1 Characteristics of the MDS patients ($N = 84$)

Variables	
Age *(years), mean ± SD*	65.82 ± 4.45
Sex *(N & %): male*	29 (34.5%)
BMI *(kg/m^2), mean ± SD*	26.31 ± 2.56
Smoking *(N & %)*	21 (25%)
Family history of PCAD *(N & %)*	6 (7.1%)
Socioeconomic status *(N & %)*	
Low	48 (57.1%)
Intermediate	31 (36.9%)
High	5 (6%)
HTN *(N & %)*	13 (15.5%)
SBP *(mmHg), mean ± SD*	132.12 ± 16.44
DBP *(mmHg), mean ± SD*	80.88 ± 10.66
Hb *(g/dL), mean ± SD*	11.44 ± 2.3
TLC *(× 10^3/L), mean ± SD*	7.1 ± 2.39
PLT *(× 10^3/L), mean ± SD*	189.4 ± 98.45
MCV *(fL), mean ± SD*	85.75 ± 3.85
FBS *(mg/dL), mean ± SD*	101.8 ± 53.04
2h-PPG *(mg/dL), mean ± SD*	150.81 ± 78.73
HbA1c *(%), mean ± SD*	5.76 ± 1.03
HOMA-IR*, mean ± SD*	2.07 ± 1.41
Total cholesterol *(mg/dL), mean ± SD*	166.83 ± 36.1
Triglycerides *(mg/dL), mean ± SD*	108.67 ± 68.85
LDL *(mg/dL), mean ± SD*	100.82 ± 34.35
HDL *(mg/dL), mean ± SD*	49.37 ± 14.34
AST *(U/L), mean ± SD*	33.12 ± 9.14
ALT *(U/L), mean ± SD*	31.52 ± 9.27
Total bilirubin *(mg/dL), mean ± SD*	0.82 ± 0.174
Serum albumin *(g/dL), mean ± SD*	3.97 ± 0.439
Serum creatinine *(mg/dL), mean ± SD*	1.03 ± .221
Urea *(mg/dL), mean ± SD*	34.78 ± 8.69
CRP *(mg/dL), mean ± SD*	6.63 ± 2.46
Homocysteine *(μmol/L), mean ± SD*	3.91 ± 4.11

N number, *%* Percentage, *SD* standard deviation, *BMI* body mass index, *HTN* hypertension, *CRP* C-reactive protein, *HOMA-IR* homeostatic model assessment for insulin resistance, *CIMT* carotid intima-media thickness, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FBS* fasting blood glucose, *2 h-PPG* 2-h post-prandial glucose, *PCAD* premature coronary artery disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Hb* hemoglobin, *TLC* total leucocytic count, *PLT* platelets, *MCV* mean corpuscular volume, *AST* aspartate transaminase, *ALT* alanine transaminase

Discussion

MDS are a diverse group of clonal myelopoietic stem-cell disorders with a higher risk of developing acute myeloid leukemia due to persistent peripheral cytopenia and morphological and functional abnormalities of hematopoietic cells, which are frequently contrasted by BM hypercellularity [7].

Accumulating evidence suggests that MDS patients, compared with individuals without MDS from the general population, have nearly a double-fold risk of arterial cardiovascular events [3].

Stimulation of atherosclerosis by beginning of physical and functional alterations in endothelial cells, culminating in endothelial dysfunction, is the mechanism of raising the cardiac risk [8, 9]. Also, clonally derived cells in MDS carry several point mutations as TET2 and ASXL1. These mutations lead to activation of Janus-associated kinase (JAK) which regulates production of proinflammatory cytokines involved in the process of atherosclerosis [10].

CHIP, a pre-MDS state, has explained a new mechanism for atherosclerotic arterial disease. Mutations in ASXL1, TET2, and DNMT3A have been linked to 1.9 times greater risk of coronary heart disease compared to noncarriers of CHIP mutations [11].

The striking feature of our study is the significantly increased CIMT, as an indicator of atherosclerosis, and inflammation markers as CRP in MDS patients supporting increased risk for CVD in these patients.

According to de Gatta et al., 36 patients with low-risk MDS were recruited from 2016 to 2017, with a mean age of 76 ± 10 years, 53% males. Thirty-one patients (84%) were in transfusion dependency. A total of 90.9% had CV risk factors (CVRFs), and 36% suffered of previous heart disease. As a result of this first cardiac assessment, 15 patients (42%) required modifications in their cardiovascular treatment, and most of cases needed to start cardiovascular treatment [12].

Faber et al. carried out a retrospective investigation on 263 patients with MDS. Cases were examined for vascular events, which were determined to be cerebral

Table 2 Comparison between patient and controls regarding demographic, cardiovascular risk, and homocysteine

	Cases (N = 84)	*Controls (N = 84)*	*Test of significance*	*P*
BMI *(kg/m²)* *Mean ± SD*	26.31 ± 2.56	26.87 ± 2.39	1.47	0.145
SBP *(mmHg)* *Mean ± SD*	132.12 ± 16.44	124.54 ± 10.67	**3.54**	**.001**
DBP *(mmHg)* *Mean ± SD*	80.88 ± 10.66	78.56 ± 8.98	1.53	0.127
FBS *(mg/dL)* *Mean ± SD*	101.8 ± 53.04	87.77 ± 18.64	**2.29**	**.023**
2h-PPG *(mg/dL)* *Mean ± SD*	150.81 ± 78.73	127.6 ± 25.17	**2.57**	**.011**
HbA1c *(%)* *Mean ± SD*	5.76 ± 1.03	5.58 ± 0.643	1.36	0.176
HOMA-IR *Mean ± SD*	2.07 ± 1.41	1.83 ± 0.431	1.49	0.138
Total cholesterol *(mg/dL)* *Mean ± SD*	166.83 ± 36.1	153.78 ± 31.44	**2.5**	**.013**
Triglycerides *(mg/dL)* *Mean ± SD*	108.67 ± 68.85	91.64 ± 27.34	**2.11**	**.037**
LDL *(mg/dL)* *Mean ± SD*	100.82 ± 34.35	89.25 ± 26.73	**2.44**	**.016**
HDL *(mg/dL)* *Mean ± SD*	49.37 ± 14.34	47.05 ± 6.98	1.33	0.184
CRP *(mg/dL)* *Mean ± SD*	6.63 ± 2.46	1.78 ± 0.57	**MW 632**	**< 0.005**
Homocysteine *(µmol/L)* *Mean ± SD*	3.91 ± 4.11	3.52 ± 2.48	MW 264	0.212

N number, *%* Percentage, *SD* standard deviation, *BMI* body mass index, *CRP* C-reactive protein, *HOMA-IR* homeostatic model assessment for insulin resistance, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FBS* fasting blood glucose, *2h-PPG* 2-h post-prandial glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate transaminase, *ALT* alanine transaminase, *MW* Mann–Whitney test

Table 3 Comparison between patient and controls regarding CIMT

	Cases (N = 84)	*Controls (N = 84)*	*Test of significance*	*P*
Right CIMT *(mm)* *Mean ± SD*	0.851 ± 0.291	0.684 ± 0.137	**4.76**	**< 0.001**
Left CIMT *(mm)* *Mean ± SD*	0.899 ± 0.343	0.726 ± 0.166	**4.16**	**< 0.001**

CIMT Carotid intima-media thickness

vascular accident (CVA), peripheral vascular disease (PVD), or coronary artery disease (CAD) by imaging or procedure, which observed a 27% global incidence of vascular disease. The incidence of vascular events by IPSS-R categories was evenly divided among low (23.7%), moderate (22%), high (25.4%), and very high (23.7%) risk disease, with the exception of very low risk disease (5.1%). One or more vascular events occurred in 63 MDS patients; of them, 55 had verified CAD, 7 had CVA, and 10 had PVD. In addition, 20% of the 63 patients who experienced vascular events did so after receiving a diagnosis of MDS; 5 of these patients experienced vascular events both before and after receiving the diagnosis. Patients with vascular disease demonstrated a tendency towards a poorer overall survival of 19.5 versus 24.5 months throughout the entire sample, as was expected [13].

Being a hematopoietic stem cell disorder, MDS is always associated with cytopenia that is either unilineage or multilineage. Chronic anemia was a common feature in our studied MDS cases, and some of them were transfusion dependent. Diseases associated with chronic anemia usually increase the risk of CVD in their host. This can be confirmed by the elevated value of CIMT in these patients as in Efat et al., which measured CIMT (as a biomarker for subclinical atherosclerosis) in a cohort of transfusion-dependent beta-thalassemic adults to explore their possible correlations with clinical, hematological, and laboratory variables and to reveal the association between risk factors and atherosclerosis. The study showed that CIMT was more in cases by median of 0.08 cm on both sides than in controls (median of 0.04 cm) of highly statistically significant value [14].

Table 4 Correlation between carotid intima-media thickness (CIMT) and other parameters in MDS patients

Variable	*CIMT*	
	R	*P*
Age	0.304	.068
BMI	0.242	0.148
Hemoglobin	0.309	.062
TLC	**0.359**	**.029**
Platelets	.080	0.640
MCV	− 0.139	0.410
FBS	.014	0.936
2h-PPG	.030	0.861
HbA1c	− .092	0.589
HOMA-IR	**0.301**	**.005**
Total cholesterol	**0.268**	**.014**
Triglycerides	**0.319**	**.003**
LDL	0.115	0.499
HDL	− .0217	0.198
CRP	**0.292**	**.007**
Homocysteine	0.190	0.260

N number, %Percentage, *SD* standard deviation, *BMI* body mass index, *HTN* hypertension, *Hs-CRP* high-sensitive C-reactive protein, *HOMA-IR* homeostatic model assessment for insulin resistance, *CIMT* carotid intima-media thickness, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *FBS* fasting blood glucose, *2h-PPG* 2-h postprandial glucose

We also found a significant positive correlation between CIMT and blood level of cholesterol, TG, HOMA-IR, Hs-CRP, and TLC in MDS cases.

Overall, 13,972 patients with incident diagnosis of MDS were identified according to Adrianzen Herrara et al., primarily men (55.2%), non-Hispanic whites (82.1%), and residents of metropolitan areas (82.5%) (*IQR*, 78–87). The median age at diagnosis was 82 years. Most (60.8%) had an illness with an intermediate risk. The median Charlson Comorbidity Index CCI score before to diagnosis was 0 (*IQR*, 0–2). A total of 9047 MDS patients were matched 1:1 with a propensity-matched non-cancer control group that took into account factors like age, gender, race, and place of residence. Incidence of CVD over the course of 5 years was 17% in MDS patients and 13% in non-cancer controls. In a multivariate regression study that took into account comorbidities, age, and gender, compared to controls, MDS was linked to a higher risk of cardiovascular disease CVD (*HR*, 1.2; 95% *CI*, 1.2–1.3). MDS was found to be substantially linked with an elevated risk of myocardial infarction MI in multivariate secondary outcome analysis (*HR*, 1.4; 95% *CI*, 1.2–1.5) but not cerebrovascular accident CVA (*HR*, 1.01; 95% *CI*, 0.89–1.15). Patients with lower comorbidity loads (CCI scores 1), in whom the 5-year incidence of MI quadrupled compared to controls, were more significantly affected by MDS than controls. After eliminating RBC transfusion-dependent

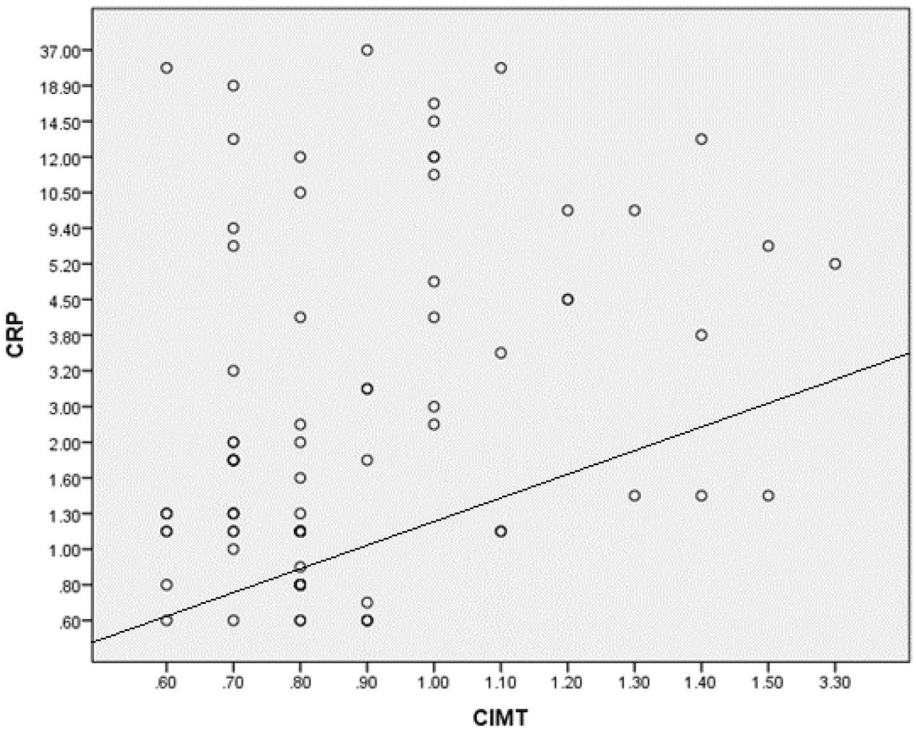

Fig. 1 Corelation between CIMT and CRP

MDS patients and their matched controls, the multivariate analysis was performed once again to take into account anemia as an etiologic factor of MI. MDS continued to have a substantial impact on the risk of MI in this sample. When compared to controls, MDS patients had significantly lower survival after a CVD event. MDS was linked to a higher mortality risk after CVD events in multivariate regression adjusted for age, gender, and comorbidities, and this effect was significant in MDS patients with both MI and CVA [5].

Our results for serum CRP level was significantly higher in studied MDS patients compared to controls which means that MDS is increasingly associated with inflammation.

Baba et al. conducted a retrospective analysis of 90 patients with low-risk MDS. They examined the prognostic relevance of CRP and known prognostic factors at diagnosis. Increased serum CRP (≥0.58 mg/dL) was associated with poor survival (hazard ratio [HR]: 17.63, 95% confidence interval [CI] 5.83–53.28, $P<0.001$) both overall and among the 73 patients with low-risk MDS as defined by the revised IPSS (*HR*: 28.05, 95% *CI* 6.15–128.04, $P<0.001$). In patients with low-risk MDS, serum CRP levels can indicate clonal hematopoiesis and non-hematological comorbidity and may predict a poor prognosis [15].

According to Hassan et al., serum levels were measured in 49 patients for TNFα and IL-10 in patients diagnosed as having MDS. Also, these inflammatory cytokines had been measured in 46 apparently healthy participants as matched controls for the study. There was a statically significant difference between MDS patients and control group according to the results of serum level of TNF-α and IL-10. They were higher in MDS patients. TNF-α was higher in MDS with multilineage dysplasia and MDS unclassifiable than the others. And IL-10 was higher in MDS with excess blasts 1 (MDS-EB1) and MDS with excess blasts 2 (MDS-EB2) than the others.

There were no positive correlations of serum level of TNF-α, IL-10 and any of age, hemoglobin level, leukocytes, platelets, ferritin, ESR, and LDH. But there was an inversely positive correlation between serum level of TNF-α and IL-10 and MDS patients [16].

Our case–control study on 186 individuals revealed that markers of dyslipidemia (as cholesterol, TG, and LDL) were higher in MDS patients than controls, and hence, they have higher risk to atherosclerosis than individuals without MDS. According to Yang et al., 39 adult patients with hematological disorders or malignancies include patients with MDS ($n=8$), patients with AML ($n=9$), patients with chronic myeloid leukemia CML ($n=11$), and patients with iron deficiency anemia IDA ($n=11$). They were compared to nine healthy controls. According to the ELISA data, there were differences in the plasma LDL levels between the groups, with AML and CML having significantly higher levels than the control group. While the average plasma LDL levels in the MDS and IDA groups were equivalent to those in the healthy controls, the average values in the AML and CML groups were significantly higher [17].

According to Qiao et al., 5422 of the 11,071 MDS patients at the MD Anderson Cancer Centre who were diagnosed and treated between 2003 and 2020 had at least one measurement of their lipid profile, CRP, or HS-CRP. They were 59.4% male and had an average age of 56 (+12). Acute leukemia was found in 62.2% ($n=3375$) of MDS patients through follow-up. They examined the test results of 2047 (37.2%) MDS patients with AML with those who did not develop the disease. In terms of the continuous variables, MDS patients who developed acute leukemia had lower levels of HDL and LDL and greater levels of triglycerides and VLDL than those who did not [18].

The mean SBP, FBG, and 2 h-PPG were higher in our studied MDS cases compared to controls, which means that MDS is associated with increased risk of hypertension and DM and hence increased risk of CVD.

Forty-four MDS patients were studied according to Kqiku et al. Six patients had elevated SPAP vs. 38 patients with normal values [19]. According to Liapis et al., retrospective data from 2972 individuals with MDS, myeloproliferative neoplasms, and low-blast-count acute myeloid leukemia (AML) revealed that 108 patients had CVD, while 723 patients passed away from other causes. The median OS and LFS of patients in the CVD death group were 30.0 months (95% *CI*, 23.0–37.0) and 29.0 months (95% *CI*, 21.9–36.1) after a median follow-up of 50.0 months (range 46.3–53.7), whereas the median OS and LFS of patients in the non-CVD death group were 20.0 months (95% *CI*, 18.2–21.8) and 17.0 months (95% *CI*, 15.4–18.6) [20].

Limitations

Our patients are few in number and come from just one nearby hospital. All patients were receiving lengthy therapy that might have had an impact on the results and also a limited age group.

The comparisons are undoubtedly disturbed by the fact that some of the individuals we included had diabetes mellitus and hypertension. Additionally, there were financial restrictions so we could not do a cytogenetics studies to MDS patients; hence, we did not have information regarding the risk stratification of MDS in the studied patients (IPSS score).

In order to counteract our findings, additional studies involving individuals with MDS from different classes (newly diagnosed & transformed) are suggested.

Conclusion

According to the results of our investigations, estimated CIMT (Rt. & Lt.) is significantly higher in patients compared to controls. In addition, CRP is significantly higher in patients compared to controls. Dyslipidemia was statistically significant in MDS patients. Homocysteine level is slightly higher in patients compared to controls but of no statistical significance. Finally, we found a significant positive correlation between CIMT and the following parameters: cholesterol level, TG level, HOMA-IR, Hs-CRP, and TLC in the studied group of patients. Our results point to increased value for inflammatory biomarkers in MDS and suggests a higher risk of CVD in MDS patients.

Authors' contributions

AE and RW wrote the manuscript and analyzed the data. FAE and AE performed data collection and manuscript preparation. SR performed radiological studies and analyses. SS and RA were responsible for the selection and follow-up of patients. All authors revised the study and reviewed the article.

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Availability of data and materials

Data are available upon request by contacting the corresponding author (Dr. Alaa Efat).

Declarations

Ethics approval and consent to participate

All patients and normal controls were consented according to IRB approved protocol before being subjected to inspection and inquiry. Every procedure was carried out in compliance with the institutional research committee's ethical standards. The faculty of medicine's ethics committee gave the study the approval (2021).

Competing interests

The authors declare that they have no competing interests.

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