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Research Article / Araştırma Makalesi

Bone Marrow Examinations in 85 Years or Older Geriatric Patients: Indications, Morbidity and Diagnosis.

Seksenbeş Yaş ve Üzerindeki İleri Yaşlı Hastalarda Kemik İliği Değerlendirilmesi: Endikasyonlar, Morbidite ve Tanı

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Abstract

As a result of the population aging, the incidence of both hematologic and non-hematologic diseases of elderly gets higher, requiring bone marrow (BM) aspirations and biopsies be implemented also in the geriatric patients. Our aim in this study is to address BM examination in the geriatric patients aged 85 and over, describing its indications and morbidity and discussing the established diagnoses and outcomes of applied therapies based on BM examinations in comparison to the available literature which is actually limited in number particularly in this patient group. We have retrospectively reviewed the BM aspiration/biopsy results of 114 patients aged ≥ 85 years who were followed-up by hematology department of a university hospital from 2010 to 2020. The patients were selected through the internal data handling system of the hospital using the entry codes corresponding to BM aspiration and biopsy and those at the age of 85 or older were identified. Demographic features, primary diagnosis, any comorbidities, complete blood count (CBC) details, erythrocyte sedimentation rate (ESR), red blood cell indices, C-reactive protein (CRP), serum ferritin, vitamin B12, and folic acid levels, any abnormal results in serum biochemistry testing, the indication(s) for and the result(s) from BM aspiration/biopsy, and the treatments applied based on those result(s) were recorded for each patient as well as the rates of and reasons for mortality. In our cohort of 114 patients with a mean age of 86.3±1.7 (85-93) years, 64.9% (n=74) were males. None of the patients experienced any serious complication during BM aspiration and biopsy. First three indications in our cohort for BM aspiration/biopsy in decreasing order of frequency were cytopenia in 48.2% (n=55), anemia + elevated ESR in 18.4% (n=21), and leukocytosis + anemia + thrombocytopenia in 15.8% (n=18). BM aspiration/biopsy results gave rise to a pathologic or hematologic diagnosis in 85.9% (n=98) and 78.9% (n=90) of patients, respectively. Most frequent hematologic malignancies were myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and multiple myeloma (MM). Kaplan-Meier analysis revealed hemoglobin (Hb) and LDH levels as prognostic factors with an impact on mortality. Prognostic factors with an impact on mortality based on multivariate stepwise Cox regression analysis, on the other hand, were uric (p= 0.018, hazard ratio (HR)= 1.134, 95% confidence interval (CI) = 1.022-1.258), LDH (p=0.092, HR=1.001, 95% CI= 1.000-1.002), and platelet levels (p=0.007, HR=1.000, 95% CI=1.000-1.000). BM examination should definitely be performed in patients aged ≥ 85 years, particularly in the event of cytopenia, unexplained anemia, and elevated ESR both for diagnostic purposes and to prolong life expectancy through administration of modified therapies depending on the performance status. In such patients uric acid, LDH and platelet levels should be closely followed-up as independent prognostic variables which effect mortality.

Keywords: hematology, geriatrics, bone marrow examination, cytopenia

Özet

Yaşlı nüfustaki artışla birlikte, yaşlı nüfusta görülen hematolojik ya da hematolojik dışı hastalıkların insidansında da bir artış gözlenmekte ve geriatrik hasta grubunda da kemik iliği aspirasyon ve biyopsi işlemi endikasyonu gerekli hale gelmektedir Çalışmamızın amacı, 85 yaş ve üzerindeki geriatrik hastalarda kemik iliği (Kİ) değerlendirme işleminin endikasyonlarını tanımlamak, morbiditesini ortaya koymak ve işlem sonucunda elde edilen tanıların ve uygulanan tedavi sonuçlarının özellikle geriatrik yaştaki hasta grubunda yapılmış az sayıdaki diğer çalışmalarla birlikte karşılaştırarak literatüre katkı sağlamaktır. 2010-2020 yılları arasında Üniversite hastanesi hematoloji bölümünde takipleri ve Kİ aspirasyon/biyopsisi yapılmış olan 85 yaş ve üstü olan 114 hastanın sonuçları retrospektif olarak değerlendirildi. Hastalar hastanenin bilgi işlem servisinden Kİ aspirasyon ve biyopsi giriş kodları kullanılarak ve yaşları 85 yaş ve üzeri olacak şekilde tespit edildi. Hastaları demografik özellikleri, primer tanıları, komorbiditeleri, ayrıntılı hemogram sonuçları, eritrosit sedimentasyon hızı (ESH), eritrosit indeksleri, C- reaktif protein (CRP), serum ferritin,vitamin B12, folik asit düzeyleri, anormal serum biyokimya sonuçları, kemik iliği aspirasyon/biyopsi endikasyonları, sonuçları ve sonuçlarda saptanan hematolojik hastalık için kullanılan tedaviler, mortalite oranları ve nedenleri kaydedildi. 114 hastanın %64.9'u (n=74) erkek, ortalama yaşları 86.3±1,7 (85-93) yıl idi. Hiçbir hastada kemik iliği aspirasyon ve biyopsi işlemi sırasında ciddi bir komplikasyon gelişmedi. Kemik iliği aspirasyon/biyopsi endikasyonları ilk 3 sırada; %48.2'sinde (n=55) sitopeni, %18.4'ünde (n=21) anemi+eritrosit sedimentasyon hızı yüksekliği, %15.8'inde (n=18) lökositoz+anemi+trombositopeni idi. 114 hastanın %85.9'unun (n=98) kemik iliği aspirasyon/biyopsi sonucu patolojik saptandı. %78.9'unda (n=90) ise hematolojik bir tanı saptandı. En sık saptanan hematolojik maligniteler myelodisplastik sendrom (MDS), akut myeloid lösemi (AML) ve multiple myeloma (MM) idi. Multivariate Stepwise Cox regresyon analizine göre mortalite üzerine etkili prognostik faktörler; ürik asit (p= 0.018, HR= 1.134 95% CI: 1.022-1.258), laktat dehidrogenaz (LDH) düzeyleri (p=0.092, HR= 1.001, 95% CI: 1.000-1.002), trombosit düzeyleri (p=0.007, HR= 1.000, 95% CI: 1.000-1.000) idi. 85 yaş ve üstü yaşlı hastalarda özellikle sitopeni ve açıklanamayan anemi ve ESH yüksekliği varlığında, tanı koyabilmek ve performans durumuna göre modifiye tedaviler verilerek yaşam süresini uzatmak için kemik iliği değerlendirmesi mutlaka yapılmalıdır. Bu hastalarda ürik asit, LDH ve trombosit düzeyleri mortalite üzerine etkili bağımsız birer prognostik değişken olarak takipte yerini almalıdır

Anahtar Kelimeler: Çocuk, karaciğer nakli, canlı aşılama

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1. Introduction

Bone marrow (BM) examination is an essential investigation method for the diagnosis and treatment of various blood and BM disorders [1,2]. This invasive procedure is in use to diagnose various disorders, whether hematologic or not, across patients of all age groups. Although this method does not have any significant side effects, it is invasive and may cause anxiety in patients [3]. BM examination has a number of indications for which several practical guidelines are available. BM examination is recommended in cases of unexplained anemia, abnormal red blood cell indices, cytopenia(s), cytosis(es), abnormal blood smear morphology suggesting the presence of a BM pathology, suspected BM metastasis, and unexplained organomegaly, and for the purpose of diagnosis, staging and follow-up of malignant hematologic diseases [1]. With the increase in the elderly population, an increase is observed in the incidence of hematological or non-hematological diseases in the elderly population, and the indication for bone marrow aspiration and biopsy procedure becomes necessary in the geriatric patient group [4]. There is a limited number of published studies on BM aspiration and biopsy examination conducted solely in geriatric age group [4-6].

Our aim here is to identify BM examination in the geriatric patients aged 85 and over by describing its indications and morbidity and by discussing the established diagnoses and outcomes of applied therapies based on BM examinations in comparison to the available literature which is actually limited in number particularly in this patient group.

2. Materials and Methods

Patient selection

This study included 114 patients who were followed-up by hematology department of a university hospital from January 2010 to January 2020 and underwent BM aspiration/biopsy at the age of ≥ 85 years. The patients were selected through the internal data handling system of the hospital using the entry codes corresponding to BM aspiration and biopsy and those at the age of 85 or older were identified. Patient results were obtained retrospectively from the patient files or the digital records. Age, gender, primary diagnosis, names of any comorbidities, complete blood count (CBC) details, erythrocyte sedimentation rate (ESR), red blood cell indices, C-reactive protein (CRP), serum ferritin, vitamin B12, and folic acid levels, any abnormal results in serum biochemistry testing, serum immunoglobulin levels and serum protein electrophoresis results, if any, organomegaly status (hepatomegaly, splenomegaly), mortality, if any, and its cause, overall survival (OS) following the BM examination, and the indication(s) for and the result(s) from BM aspiration/biopsy, and the treatments given for the hematologic disease indicated by those result(s) were recorded for each patient. Results of cytogenetic testing were not included into this study.

Definition of cytopenia

A count of hemoglobin <13g/dL in men and hemoglobin <12g/dL in women was accepted as anemia, a leukocyte count of<4000/mm3 was accepted as leucopenia, absolute neutrophil count of <1500/mm3 was accepted as neutropenia, and a platelet count of <100.000/mm3 is accepted as thrombocytopenia. The presence of any one of these values was considered as meeting the criterion for cytopenia.

BM aspiration and biopsy examination

BM aspirates and biopsies were taken from posterior superior iliac spine in accordance with ICSH guidelines [1]. The BM smear preparation was evaluated by experienced hematologists. The BM smear preparation viewed under low power magnification (x10) to determine the number and cellularity of particles, the number of megakaryocytes, and to scan for clumps of abnormal cells incidence. The details of the BM smear at the back of the particles were evaluated at higher magnification (ie, x40, x100). In the diagnosis of hematologic diseases, BM aspiration was evaluated as well as flow cytometric analysis in appropriate patients.

The study was approved by Eskişehir Osmangazi University Ethics Committee in April 2020, with Protocol Number 25403353-0.50.99-E.51579.

Statistical Analysis

Continuous data were depicted as mean ± standard deviation, median (Q1; Q3), while categorical data were depicted as percentage (%).

Shapiro Wilk test was used to compare the conformity of the data to normal distribution. Independent sample t test analysis was used to compare the groups with normal distribution when there were two groups. For the comparison of groups that do not have a normal distribution, Mann-Whitney U test was used. In the analysis of cross tables, Pearson Chi-square, Pearson Exact Chi-square, Yate's Chi-square, Fisher's Exact Chi-square analyses were applied. Cox regression method with stepwise analysis was used to identify the prognostic variables effective on survival. Kaplan- Meier test was applied to compare survivals of two groups (with Log-rank test to assess significant of difference). P value ≤ 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program.

3. Results

During the time period of 2010-2020, 114 patients underwent BM examination at an age of 85 years or above. Mean age of cohort at the time of procedure was 86.3±1.7 (85-93) years and was consisting of 35.1% (n=40) females and 64.9% (n=74) males. (Demographic characteristic and laboratory results of patients are shown in table 1). A previous disease was known in 85.9% (n=98) of patients, whereas 14% (n=16) had no previously known disease. When ranked by decreasing frequency, first 5 primary diagnoses were diabetes mellitus (DM) in 14.9% (n=17), chronic kidney disease (CKD) in 15.3% (n=15), hypertension (HT) in 13.2% (n=13), coronary artery disease (CAD) in 8.1% (n=8), and chronic obstructive pulmonary disease (COPD) in 7.1% (n=7) (Rates of primary diseases in patients who had undergone BM examination are listed in table 2).

Table 1. Demographics and laboratory features of 114 patients who were underwent bone marrow examination

	Whole group
n	114
Age, mean±SD,(min-max) years	86.3±1.7 (85-93)
Sex (F/M), n	40/74
Laboratory during BM examination, mean±SD, (min-max)	
Hb level, g/dL	9.5±2.4 (3.3-16.5)
MCV level,/fL	90.71±9.5 (65.6-125)
WBC level,/mm^3	23043.8±37801.3 (270-243080)
ANC level,/mm^3	10979.6±19737.5 (0-111000)
ALC level,/mm^3	5475.2±12260.3 (100-73700)
AMC level,/mm^3	5778.4±20224.7 (0-181750)
AEC level,/mm^3	442.6±3243 (0-32800)
PLT level,/mm^3	153000±244132.9 (3000-2200000)
MPV level,/fL	9.03±1.56 (5.8-11.9)
ESR level,mm/h	61.4±41.4 (2-148)
CRP level,mg/dl	16.8±35.7 (0.32-227.2)
Ferritin level,ng/ml	414.2±528 (20-3734)
Vitamin B12 level,pg/ml	751.9±624.3 (55-2000)
Folic acit level, ng/ml	7.85±5.25 (1.53-20)
BUN level,mg/dl	34.9±25.3 (10.4-181.6)
Cr level,mg/dl	1.74±1.58 (0.49-11.23)
LDH level,U/L	674.8±761.9 (163-5774)
Uric acit level,mg/dl	7.1±3.2 (1.9-21)
IgG level, mg/dl	1386.31±835.7 (153-4160)
IgA level, mg/dl	559.8±1166.6 (17-6120)
IgM level, mg/dl	481.6±1619 (15.6-7810)
Deaths n, %	86, 75.4%

Hb; hemoglobin, MCV; mean corpuscular volume, WBC; White blood cell, ANC; absolute neutrophil count, ALC; absolute lymphocyte count, AMC; absolute monocyte count, AEC; absolute eosinophil count, PLT; platelet, MPV; mean platelet volume, ESR; erythrocyte sedimentation rate, CRP; c-reactive protein, BUN; blood urea nitrogen, Cr; creatinine, LDH; lactate dehyrdogenase, Ig; immunoglobulin

Table 2. Distribution of 114 patients with bone marrow examination according to primary disease diagnosis.

Disease	n=114
Primary diseases, n (%)	98 (85.9%)
Diabetes mellitus	17 (17.3%)
Chronic renal failure	15 (15.3%)
Hypertension	13 (13.2%)
Coronary artery disease	8 (8.1%)
Chronic obstructive pulmonary disease	7 (7.1%)
Colon cancer	3 (3.1%)
Benign prostatic hypertrophy	3 (3.1%)
Cerebrovascular disease	3 (3.1%)
Prostate cancer	3 (3.1%)
Heart failure	2 (2%)
Rheumatoid arthritis	2 (2%)
Psoriasis	2 (2%)
Non-Hodkgin lymphoma	2 (2%)
Stomach cancer	2 (2%)
Other causes	16 (16.3%)

Other causes; over cancer, myelodysplastic syndrome, malignant melanom, bladder cancer, dementia, osteoporosis, osteoarthritis, polycythemia vera, emphysem, parkinson, chronic myeloid leukemia, cardiomyopathy, atypical hemolytic uremic syndrome

Of 114 patients, 86.8% (n=99) had anemia. We could access the mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values for 95% (n=94) of 99 anemic patients. When morphology of anemia was investigated in those 94 patients, 75.5% (n=71) had normochromic, normocytic anemia; 9.6% (n=9) had hypochromic, microcytic anemia; and 14.8% (n=14) had macrocytic anemia.

Leukocyte measurements were available in 97.4% (n=111) of 114 patients. Accordingly, 36.9% (n=41) had leukocytosis and 26.1% (n=29) had leukopenia. We could reach absolute neutrophile and platelet counts of 98.2% (n=112) of patients which demonstrated 20.5% (n=23) had neutropenia and 67.9% (n=76) had thrombocytopenia. Absolute monocyte counts were retrieved in 88.6% (n=101) of patients. Monocytosis was detected in 30.7% (n=31) of patients. LDH levels were accessed in 86.8% (n=99) of our cohort , of whom 81.8% (n=81) had increased LDH.

Cytopenia, in at least one lineage, was detected in 93.9% (n=107) of our 114 patients.

Among the 48.2% (n=55) patients whose indication for BM aspiration/biopsy was cytopenia, subtype was determined as bicytopenia, pancytopenia, and isolated cytopenia in 27.2% (n=15), 49% (n=27), and 23.6% (n=13), respectively. BM findings were indicating dysplasia in 48.2% (n=55) of patients.

At least one comorbid disease was determined in 83.3% (n=95) of our patients who were aged 85 years or older. Most common comorbidities and their respective percentages were: HT: 53.6% (n=51), DM: 34.7% (n=33), CAD: 29.5% (n=28), CKD: 20% (n=19), and COPD: 16.8% (n=16).

Of our patients, 42.1% (n=48) were on antiaggregants and 42.1% (n=48) were on anticoagulants (low molecular weight heparin, warfarin, or novel oral anticoagulant). None

of the patients experienced any serious complication during BM aspiration and biopsy.

Mean size of BM biopsy collected from the patients were 1.08±0.45 (0.3-2.3) cm. BM cellularity, on average, was 51.2%±25.7% (0-100).

As it was indicated, serum immunoglobulin level measurement and serum protein/immunofixation electrophoresis was conducted in 32 patients, results of which revealed monoclonal gammopathy in 59.4% (n=19) and polyclonal gammopathy 25% (n=8).

In our study cohort, BM aspiration/biopsy results gave rise to a pathologic or hematologic diagnosis in 85.9% (n=98) and 78.9% (n=90) of patients, respectively. A hematologic diagnosis was established in 90 patients, of which 88.8% (n=80) were a malign hematologic diagnosis. When a hematologic diagnosis was made, 96.6% (n=87) of the patients received a treatment for that hematologic diagnosis and 41.3% (n=36) received chemotherapy treatment.

Indications for BM aspiration/biopsy

The breakdown of BM aspiration/biopsy indications by number of patients was as follows: cytopenia in 48.2% (n=55), anemia+elevated ESR in 18.4% (n=21), leukocytosis+ anemia+thrombocytopenia in 15.8% (n=18), anemia+lymphocytosis+thrombocytopenia in 2.6% (n=3), anemia+leukocytosis+elevated ESR in another 2.6% (n=3), anemia+proteinuria+elevated ESR in yet another 2.6% (n=3), anemia+monoclonal gammopathy in 1.8% (n=2), lymphocytosis in another 1.8% (n=2), and other causes in 6.1% (n= 7) (Indications for BM examination are given in table 3).

Table 3. Indications for bone marrow examination of 114 patients

BM examination causes	n(%)
Cytopenia	55(48.2%)
Pancytopenia	27(49%)
Bicytopenia	15(27.2%)
Anemia and thrombocytopenia	13(86.6%)
Anemia and neutropenia	2(15.4%)
Isolated cytopenia	13(23.6%)
Isoletaed neutropenia	3(23.1%)
Isoletaed thrombocytopenia	7(53.8%)
Isolated leucopenia	1(7.6%)
Isolated anemia	2(15.4%)
Anemia and high ESR levels	21(18.4.%)
Leucocytosis and anemia and thrombocytopenia	18(15.8%)
Anemia and lymphocytosis and thrombocytopenia	3(2.6%)
Anemia and leucocytosis and high ESR levels	3(2.6%)
Anemia and proteinuria and high ESR levels	3(2.6%)
Anemia and monoclonal gammapathy	2(1.8%)
Lymphocytosis	2(1.8%)
Leucocytosis and thrombocytopenia	1(0.9%)
Follow-up staging of known lymphoma	1(0.9%)
Anemia and high ESR levels and thrombocytopenia	1(0.9%)
High ESR levels and pancytopenia	1(0.9%)
Suspicion of plasma cell myeloma after known plasmacytoma	1(0.9%)
Anemia and leucocytosis and thrombocytosis	1(0.9%)
Eosinophilia	1(0.9%)

BM; bone marrow, ESR; erythrocyte sedimentation rate

Pre-diagnosis prior to BM aspiration/biopsy

Pre-diagnosis prior to BM aspiration and biopsy were as follows: multiple myeloma (MM)/plasma cell dyscrasia in 21.9% (n=25), myelodysplastic syndrome (MDS) in 36.8% (n=42), acute leukemia in 16.7% (n=19), chronic lymphocytic leukemia (CLL) in 5.3% (n=6), immune thrombocytopenia (ITP) in 5.3% (n=6), involvement of lymphoma in 2.6% (n=3), chronic myelomonocytic leukemia (CMML) in 2.6% (n=3), Waldenstrom's macroglobulinemia (WM) in 0.9% (n=1), chronic myeloid leukemia (CML) in 0.9% (n=1), hairy cell leukemia (HCL) in 0.9% (n=1), amyloidosis in 0.9% (n=1), BM metastasis of colon cancer in 0.9% (n=1), essential thrombocytosis (ET) in 0.9% (n=1), post–polycythemia vera myelofibrosis (post-PV MF) in 0.9% (n=1), BM metastasis of stomach cancer in 0.9% (n=1), methotrexate-induced BM suppression in 0.9% (n=1), and hypereosinophilic syndrome (HES) in 0.9% (n=1).

Results of BM aspiration/biopsy

In our study cohort, BM aspiration/biopsy results gave rise to a pathologic or hematologic diagnosis in 85.9% (n=98) and 78.9% (n=90) of patients, respectively. A hematologic diagnosis was established in 90 patients, of which 88.8% (n=80) were a malign hematologic diagnosis. The results of BM examinations of our patients were as follows: MDS in 19.3% (n=22), acute myeloid leukemia (AML) in %14.9 (n=17), normal in 14% (n=16), MM in 10.5% (n=12), ITP in 7% (n=8), MDS refractory anemia with excess blasts (RAEB) type-2 in 5.3% (n=6), reactive plasmacytosis in 5.3% (n=6), CLL in 3.5% (n=4), MDS-RAEB-type 1 in 2.6% (n=3), CMML in 2.6% (n=3), WM in 1.8% (n=2), marginal zone lymphoma (MZL) in 1.8% (n=2), B-cell non-Hodgkin's lymphoma (NHL) in 1.8% (n=2), methotrexate-induced BM hypocellularity in 1.8% (n=2), CML in 0.9% (n=1), B-cell acute lymphoblastic leukemia (ALL) in 0.9% (n=1), HCL in 0.9% (n=1), ET in 0.9% (n=1), post-PV MF in 0.9% (n=1), monoclonal gammopathy of undetermined significance (MGUS) in 0.9% (n=1), erythroid hyperplasia (EH) in 0.9% (n=1), AA amyloidosis in 0.9% (n=1), and HES in %0.9 (n=1). (Characteristics of 80 patients who were diagnosed with a malignant hematologic pathology based on the evaluation of BM aspiration/biopsy are given in table 4).

Mortality rates and prognostic factors

Starting from the day BM aspiration/biopsy was collected from the patients, median OS time was 180 (range 28.2-547.5) days. During the course of study, 24.6% (n=28) of patients survived, whereas 75.4% (n=86) died. We have identified the reason for mortality was sepsis in 18.6% (n=16), sepsis+pulmonary infection in 15.1% (n=13), progression of primary disease in 5.81% (n=5), cerebrovascular disease (CVD) in 4.65% (n=4), intracranial hemorrhage in 2.32% (n=2), intracranial hemorrhage+pneumonia+disseminated intravascular coagulation (DIC) in 1.16% (n=1), femoral fracture+pulmonary embolism+CVD in 1.16% (n=1), ovarian cancer+multi-organ failure in 1.16% (n=1), progression of AML+atrial fibrillation (AF)+ pneumonia in 1.16% (n=1), sepsis+AF in 1.16% (n=1), massive gastrointestinal (GI) bleeding in 1.16% (n=1), myocardial infarction (MI)+urosepsis in 1.16% (n=1), GI bleeding+intracranial hemorrhage in 1.16% (n=1), acute cerebral infarction+cholangitis+sepsis in 1.16% (n=1), catheter infection+urosepsis in 1.16% (n=1), pancreatitis+GI bleeding in 1.16% (n=1), leukostasis+pneumonia in 1.16% (n=1), pneumonia+heart failure in 1.16% (n=1), emphysema+pneumonia in 1.16% (n=1), MI in 1.16% (n=1), heart failure+acute pulmonary edema+pneumonia+acute kidney failure in 1.16% (n=1), and no reason could be identified in 34.8% (n=30) of our patients.

Mortality was significantly higher among those with an elevated LDH level compared to the patients with lower LDH levels ($p<0.01$).

Median duration of OS was 120 (range 45.3-194.6) days in higher (abnormal) LDH group, while respective duration was 480 (range 164.4-795.5) days in lower (normal) LDH group, making a statistically significant difference ($p=0.027$) (Figure 1.A).

We also compared survival of the patients by the most common pathological BM examination results (MDS, AML, and MM). The shortest OS was in AML [median 30 (range 21.3-38.6) days] patients, the longest OS was in MDS subgroup except for elevated blast [median 360 (0-756) days] and MM subgroup had a median OS of 90 (range 0-267.6) days ($p<0.0001$) (Figure 1.B).

Table 4. Characteristics of 80 patients with malignant hematological pathology as a result of bone marrow aspiration/biopsy.

Malign hematologic disease	Indications for bone marrow examination	Preliminary diagnosis	Outcome	Treatment
MDS n=22	21 cytopenia, 1 leucocytosis and anemia and thrombocytopenia	20 MDS 2 ITP	7 alive 15 dead	Transfusion, G-CSF, IVIG, methylprednisolone, danazol, erythropoietin
MDS-RAEB-type 1 n=3	3 cytopenia	3 MDS	1 alive 2 dead	Transfusion, iron chelation therapy, 5-azacytidine
MDS-RAEB-type 2 n=6	6 cytopenia	6 MDS	2 alive 4 dead	Transfusion, iron chelation therapy, 5-azacytidine, IVIG
CMML n=3	2 leucocytosis and anemia and thrombocytopenia 1 anemia and leucocytosis and high ESR levels	3 CMML	3 dead	Transfusion, hydroxyurea, 5-azacytidine, decitabine, etoposide, IVIG
AML n=17	13 leucocytosis and anemia and thrombocytopenia 3 cytopenia 1 leucocytosis and thrombocytopenia	14 Akut leukemia 2 MDS	1 alive 16 dead	Transfusion, leukapheresis, hydroxyurea, 5-azacytidine, subcutaneous cytosine arabinoside, etoposide
B-ALL n=1	Leucocytosis and anemia and thrombocytopenia	Acute leukemia	dead	Transfusion, hydroxyurea, methylprednisolone
MM n=12	5 anemia and high ESR levels 2 anemia and monoclonal gammapathy 1 anemia and lymphocytosis and thrombocytopenia 1 anemia and high ESR levels and thrombocytopenia 1 cytopenia 1 high ESR levels and pancytopenia 1 suspicion of plasma cell myeloma after known plasmacytoma	11 MM 1 CLL	2 alive 10 dead	Transfusion, plasma exchange, bortezomib, dexamethasone, melpahalan, methylprednisolone, radiotherapy, zoledronic acid
WM n=2	1 anemia and high ESR levels 1 cytopenia	1 WM 1 MM/ plasma cell dyscrasia	2 dead	Transfusion, plasma exchange, cyclophosphamide, vincristine, methylprednisolone
MGUS n=1	Anemia and high ESR levels	MM	dead	IVIG
CLL n=4	2 lymphocytosis 1 anemia and high ESR levels 1 anemia and lymphocytosis and thrombocytopenia	3 CLL 1 ITP	2 alive 2 dead	Transfusion, chlorambucil, methylprednisolone
B-cell NHL n=2	1 anemia and lymphocytosis and thrombocytopenia 1 cytopenia	1 CLL 1 Akut leukemia	1 alive 1 dead	Transfusion, rituximab, cyclophosphamide, vincristine, methylprednisolone, G-CSF
MZL n=2	1 anemia and high ESR levels 1 anemia and leucocytosis and high ESR levels	1 CLL 1 MM/ plasma cell dyscrasia	1 alive 1 dead	Transfusion, plasma exchange, methylprednisolone
CML n=1	Leucocytosis and anemia and thrombocytopenia	CML	dead	Hydroxyurea, imatinib
ET n=1	Anemia and leucocytosis and thrombocytosis	ET	dead	Hydroxyurea, acetylsalicylic acid
Post-PV MF n=1	Anemia and leucocytosis and high ESR levels	Post-PV MF	dead	Transfusion, ruxolitinib
HES n=1	Eosinophilia	HES	dead	Hydroxyurea, methylprednisolone
HCL n=1	Cytopenia	HCL	alive	Transfusion, cladribine

MDS; myelodysplastic syndrome, AML; acute myeloid leukemia, MM; multiple myeloma, RAEB; Refractory anemia with excess blasts, CMML;Chronic myelomonocytic leukemia, WM; Waldenstrom macroglobulinemia, NHL; non-Hodkgin lymphoma, MZL; marginal zone lymphoma, ALL; acute lymphoblastic leukemia, CML; chronic myeloid leukemia, HCL; hairy cell leukemia, ET; essential thrombocythemia, Post-PV MF; post–polycythemia vera myelofibrosis, MGUS; monoclonal gammopathy of undetermined significance, HES; hypereosinophilic syndrome, ITP; immune thrombocytopenia, ESR; erythrocyte sedimentation rate, G-CSF; granulocyte colony-stimulating factor, IVIG; intravenous immunoglobulin.

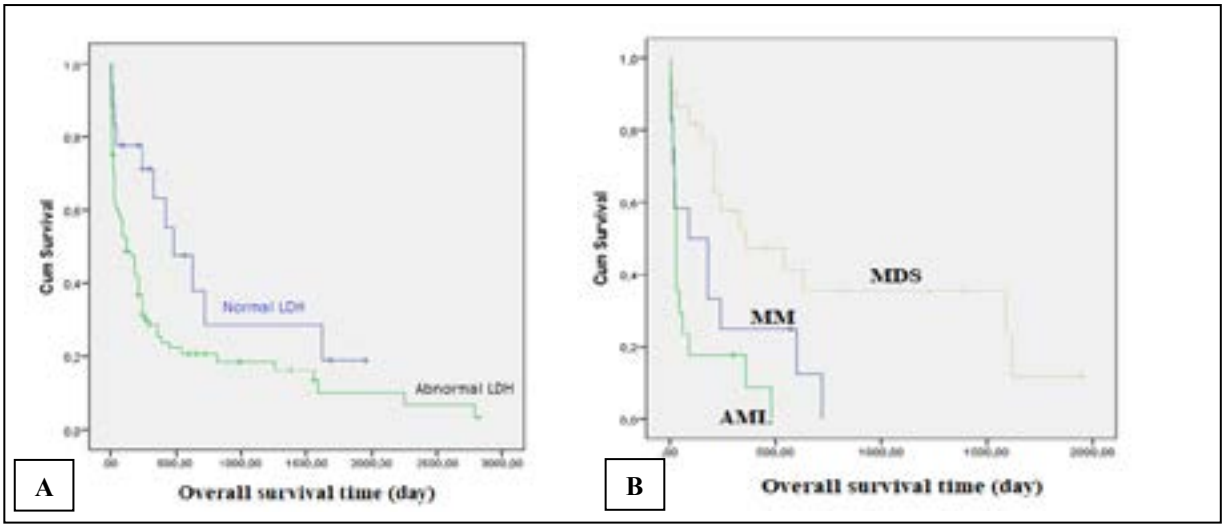

Figure 1. Overall survival curves of the 85 years and older patients based on (A) LDH levels (B) Their diagnosis.

Comparison of LDH levels of the patients with and without a pathological BM aspiration/biopsy result revealed higher LDH levels in those with pathological results, but not to a significant extent (712.1±87.1 vs 467.5±132.2, p>0.05).

Kaplan-Meier analysis identified laboratory parameters Hb and LDH level were prognostic factors effective on mortality (comparison of patients who died and who survived; mean Hb 9.1±2.2 g/dL vs 10.9±2.6 g/dL; median LDH 529 vs 262 IU/L (p=0.002, p<0.0001, respectively).

Multivariate stepwise Cox regression analysis revealed that uric acid, LDH and platelet levels were the prognostic variables that affect mortality (Table 5).

Table 5. Multivariate analysis on overall survival in 85 years and older patients undergoing bone marrow examination

Variables	Hazard ratio (95% CI)	p value
Uric acid levels	1.134 (1.022-1.258)	p= 0.018
LDH levels	1.001 (1.000-1.002)	p=0.092
Platelet levels	1.000 (1.000-1.000)	p=0.007

LDH; lactate dehyrdogenase

4. Discussion

The older the population ages, the higher the incidence of both hematologic and non-hematologic diseases of elderly gets. More than likely, we will be conducting BM aspiration/biopsy more frequently in patients of advanced age as the population gets older. There is a limited number of published studies on BM aspiration and biopsy examination conducted solely in geriatric age group [4,5]. In our study, we evaluated the bone marrow aspiration/biopsy examination process in geriatric patients aged 85 and over.

BM examination has a number of indications. BM examination is recommended in cases of unexplained anemia, abnormal red blood cell indices, presence of cytosis, suspected BM metastasis, and for the purpose of diagnosis, staging and follow-up of malignant hematological diseases [1]. Indications for BM aspiration/biopsy in infants, children as well as young and middle-aged adults may differ from those in elderly. In the general population composed of infants, children, and young and middle-aged adults, most common indication for BM examination is staging of

acute leukemia and lymphoma whereas unexplained cytopenia and anemia stands for the most frequent indications among elderly and extremely elderly [4,5,7]. In the study of Manian E. et al. conducted with patient aged 85 years and older, the most common indications were cytopenia in 36.1% and followed by thrombocytosis or leukocytosis in 14.3% (n=17), Gulati A. et al., on the other hand, stated unexplained anemia ranked at the first place in their cohort composed of ≥ 60 year-old patients [4,5]. Our study recruited 114 patients at the of 85 or above and most common indication for BM aspiration/biopsy were cytopenia taking place in 48.2% (n=55) of our patients followed by anemia+elevated ESR in 18.4% (n=21), and triad of leukocytosis+anemia+thrombocytopenia in 15.8% (n=18). In our study, the most common indication for bone marrow examination was cytopenias, accounting for almost half of the cases. Based on our review of existing literature comparing our results, we had very few elderly patients undergoing BM examination due to thrombocytosis or leukocytosis. Furthermore, the second most common indication in our cohort, namely anemia + elevated ESR, was also not alike the literature.

BM aspiration/biopsy examination is an invasive procedure used to diagnose various hematologic or non-hematologic disorders. A specific malignant hematologic diagnosis was made upon BM aspirations/biopsies in 43% and 43.3% of cases in the studies by Manian E. et al and Gulati A. et al, respectively [4,5]. In our study, 85.9% (n=98) out of 114 patients had a pathology based on their BM aspiration/biopsy results and 70.1% (n=80) were diagnosed with a specific hematologic malignancy. Our study is first of its kind with the highest ratio of specific malignant hematologic diagnosis so far in literature among patients aged 85 and over.

When BM examination is carried out due to the indication of cytopenia, the likelihood to establish a specific diagnosis is quite small in patients of advanced age who are ≥ 85 years old, in whom the highest rates of diagnosis were reported for leukocytosis and thrombocytosis [4]. Manian E. et al have advocated undergoing BM aspiration/biopsy would bring no difference in terms of clinical management or outcomes in majority of elderly patients with cytopenia and therefore suggested cytopenia should be followed-up as long as there is no suspected clonal myeloproliferative disorder [3,4]. On contrary to the literature data, we have achieved quite a high figure of specific diagnosis among our patients ≥ 85 years old who underwent BM examination due to cytopenia, and most frequently diagnosed them with low-risk or high-risk MDS. In line with our results and given its very low morbidity, we consider BM examination should be an integral part of diagnostic workup and treatment management in extremely elderly patients with cytopenia.

Anemia is very common among this patient population and has been recognized as an important cause of morbidity. Anemia may arise from a plethora of reasons in elderly including nutritional insufficiency (most often in forms of megaloblastic and micronormoblastic), chronic inflammation, chronic kidney disease, MDS as well as from an unexplained etiology in many patients [8-10]. In anemic patients of advanced age, BM aspiration/biopsy is a reliable intervention with a complication rate of < 0.05% and thus should be performed to rule out MDS and any other hematologic disorders [3,4]. In our study, anemia+elevated ESR was the second most common cause for BM aspiration/biopsy examination and specific diagnoses of MM, WM, and MZL were established quite frequently in this subgroup. None of the patients in our cohort had experienced any serious complication during BM aspiration/biopsy.

Although rare among children and young adults, the incidences of MDS and chronic myeloproliferative neoplasms (CMPNs) as well as leukemia and lymphoma are known to increase with age [11]. In their study including patients at the age of 85 and above who have underdone BM examination, Manian E. et al reported one third of the newly diagnosed cases were MDS and CMPNs [4], while two thirds of our cases were composed of MDS, AML, and MM. Dissimilar to the literature data, in our patient

cohort of BM examination patients aged ≥ 85 years, AML and MM were diagnosed more often and CMPNs were diagnosed less often.

Due to their performance status, supportive care is preferred over chemotherapy regimens in elderly with malignancies. Our literature search figured out the specific diagnoses in 79 of 119 patients aged ≥ 85 years who experienced BM aspiration/biopsy. Furthermore, we accessed follow-up details of 56.9% (n=45) of whom 44% (n=20, 9 lymphoma, 5 MM, 3 AML, 3 CMPN or MDS) were treated and only 17 were administered a modified or dose-reduced regimens due to poor performance status or drug intolerance. Eventually, all of these treatment were reported as unsuccessful [4]. In our study, on the other hand, a hematologic diagnosis was made for 90 patients leading to prescription of a treatment for that hematologic diagnosis in 96.6% (n=87) of the patients and 41.3% (n=36) of treatment receivers were given chemotherapy (Details are given in table 4). Even if a hematologic malignancy develops in extremely elderly patients, it is still possible to prolong their OS by applying dose-reduction or modified treatment regimens along with supportive care taking their performance status into account.

None of the former BM aspiration/biopsy studies conducted on elderly population so far has evaluated the OS, rates and causes of mortality, or the prognostic factors which affect mortality [4,5]. A distinct aspect of our study is we have also provided mortality rates, causes of mortality, and the prognostic variables with an impact on mortality in our patient group. Our analysis showed 24.6% (n=28) of patients survived, whereas 75.4% (n=86) died. Most frequent reason of mortality was sepsis. Hb and LDH levels were identified as prognostic variables which affect mortality. LDH, uric acid, and platelet levels were each an independent prognostic variable effective on OS. In the extremely elderly patient group, particularly in patients aged ≥ 85 years, for whom BM aspiration/biopsy is indicated and therefore BM examination is applied, it is likely that Hb, LDH, uric acid, and platelet levels will help clinicians during the follow-up of patients as factors effective on OS and mortality.

The main limitation of this study is its retrospective design. Second, the number of patients is relatively small.

Consequently, BM aspiration/biopsy procedure features out with its low complication rate in patients at the age of ≥ 85 years, as in other age groups. Therefore, clinicians should not avoid diagnostic BM examination in this age group, especially in the event of unexplained cytopenia in combination with elevated ESR, as it offers a high likelihood of specific diagnosis.

REFERENCES

1. Lee SH, Erber WN, Porwit A, Tomonaga M, Peterson LC. ICSH guidelines for the standardizations of bone marrow specimens and reports. *Int Jnl Lab Hem* 2008; 30:349-364.
2. Focosi D. Bone marrow aspiration and biopsy. *N Engl J Med* 2010;362;182-183
3. Bain BJ. Morbidity associated with bone marrow aspiration and trephine biopsy: a review of UK data for 2004. Haematologica. 2006;911293-1294.
4. Manion EM, Rosenthal NS. Bone marrow biopsies in patients 85 years or older. *Am J Clin Pathol*. 2008;130:832-835.
5. Gulati A, Mandal T, Kaushal V, Kaushik R, Thakur S. Bone Marrow Disease Profile in Geriatric Patients: An Institutional Experience. Indian *J Hematol Blood Transfus*. 2018;34:540-543.
6. Girodon F, Favre B, Carli PM, Nash N, Desbiolles N, Tatou E, et al. Minor dysplastic changes are frequently observed in the bone marrow aspirate in elderly patients without haematological disease.*Clin Lab Haematol.* 2001;23:297-300.
7. Bashawri LA. Bone marrow examination. Indications and diagnostic value. *Saudi Med J.* 2002;23:191-6.
8. Gaskell H, Derry S, Andrew Moore R, McQuay HJ. Prevalence of anaemia in older persons: systematic review. BMC Geriatr. 2008;8:1-8.
9. Pinto A, De Filippi R, Frigeri F, Corazzelli G, Normanno N. Aging and the hemopoietic system. *Crit Rev Oncol Hematol.* 2003;48:3-12.
10. Eisenstaedt R, Penninx BW, Woodman RC. Anemia in the elderly: current understanding and emerging concepts. *Blood Rev*. 2006;20:213-26.
11. Kaushansky A, Lichtman MA, Prchal JT, Levi MM, Press OW, Burns JL, et al. Williams Hematology. 9th ed. NY: McGraw Professional; 2016