PROGNOSTIČKI FAKTORI RIZIKA ZA RANU SMRT KOD BOLESNIKA SA AKUTNOM MIJELOIDNOM LEUKEMIJOM

ORIGINALNI RAD

ORIGINAL ARTICLE

PROGNOSTIC RISK FACTORS FOR EARLY DEATH IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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SAŽETAK

Uvod: Rana smrt je poznata komplikacija lečenja bolesnika sa akutnom mijeloidnom leukemijom (AML). Definisana je kao smrt koja se javlja unutar 28 dana od otpočinjanja indukcione hemioterapije.

Cilj: Određivanje kliničkih karakteristika bolesnika, faktora rizika, učestalosti i najčešćih uzroka rane smrti kod bolesnika sa AML-om.

Materijali i metode: U retrospektivnu studiju uključeno je 248 bolesnika sa dijagnostikovanom akutnom mijeloidnom leukemijom. Pri dijagnozi, evidentirane su demografske i kliničko-laboratorijske karakteristike: pol, starost, opšte funkcionalno stanje po ECOG skali, kompletna krvna slika, nivo serumske LDH, procenat blasta u perifernoj krvi i koštanoj srži, fibrinogen, PT, aPTT, D-dimer i BMI. Bolesnici su lečeni indukcionom i redukcionom hemioterapijom i palijativnom terapijom. Statistička analiza rađena je pomoću podataka iz otpusnih lista uzetih iz registara Klinike za hematologiju Kliničkog centra Srbije.

Rezultati: Rana smrt je nastupila kod 53 (21,4%) bolesnika. Pokazalo se da su prognostički faktori rizika za ranu smrt: godine starosti ($p = 0,047$), ECOG ≥ 2 ($p = 0,001$), broj leukocita ≥ 30 x 10^9/l ($p = 0,022$), vrednost LDH ≥ 450 U/l ($p = 0,029$), procenat blasta u perifernoj krvi ($p = 0,005$) i koštanoj srži ($p = 0,003$), vrednost PT ($p < 0.001$) i ISTH skor ($p = 0,018$). Najčešći uzrok rane smrti kod bolesnika od 40 – 65 godina bila je sepsa, dok je kod starijih od 65 godina to bila respiratorna insuficijencija.

Zaključak: Studija je pokazala da su godine starosti, broj leukocita, procenat blasta u perifernoj krvi i koštanoj srži, vrednost ECOG skora, LDH, PT, i ISTH skor značajni prognostički faktori rizika za ranu smrt kod bolesnika sa AML-om, a da je najčešći uzrok rane smrti kod bolesnika starosnog doba od 40 – 65 godina bila sepsa, dok je kod bolesnika starijih od 65 godina to bila respiratorna insuficijencija.

Ključne reči: akutna mijeloidna leukemija, rana smrt, faktori rizika, uzroci smrti

ABSTRACT

Introduction: Early death is a known complication in the treatment of patients suffering from acute myeloid leukemia (AML). It has been defined as death occurring within 28 days of the initiation of induction chemotherapy.

Aim: Determining the clinical characteristics of the patient, the risk factors, the frequency, and the most common causes of early death in AML patients.

Materials and methods: This retrospective study included 248 patients with diagnosed AML. At diagnosis, the following demographic and clinical-laboratory characteristics were recorded: sex, age, general functional status, i.e., performance status according to the ECOG scale, complete blood count, LDH level in the blood, percentage of blasts in peripheral blood and bone marrow, fibrinogen, PT, aPTT, D-dimer, and BMI. Patients were treated with induction and reduction chemotherapy and palliative therapy. Statistical analysis was performed using the data from the discharge summaries taken from the registers of the Clinic for Hematology of the Clinical Center of Serbia.

Results: Early death occurred in 53 (21.4%) patients. The prognostic risk factors for early death were the following: age ($p = 0.047$), ECOG ≥ 2 ($p = 0.001$), leukocyte count ≥ 30 x 10^9/l ($p = 0.022$), LDH level ≥ 450 U/l ($p = 0.022$), the percentage of blasts in peripheral blood ($p = 0.005$) and the percentage of blasts in bone marrow ($p = 0.003$), PT ($p < 0.001$), as well as the ISTH score ($p = 0.018$). The most common cause of early death in patients aged 40 – 65 years was sepsis, while in patients older than 65 years it was respiratory failure.

Conclusion: The study showed that age, the leukocyte count, the percentage of peripheral blood and bone marrow blasts, the ECOG score, LDH, PT, and the ISTH score were significant prognostic risk factors of early death in patients with AML, and that the most common cause of early death in patients aged 40 – 65 years was sepsis, while in patients older than 65 years it was respiratory failure.

Key words: acute myeloid leukemia, early death, risk factors, causes of death

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UVOD

Akutna mijeloidna leukemija (AML) je heterogena klonalna maligna bolest hematopoeznog tkiva u kojoj nezrele ćelije hematopoeze proliferišu i akumuliraju se u koštanoj srži, perifernoj krvi i drugim tkivima [1].

AML je retka maligna bolest hematopoeznog tkiva, koja se uglavnom javlja kod bolesnika starijeg životnog doba [2]. Spada u grupu bolesti sa jasno definisanim citogenetskim i imunološkim karakteristikama, koje su prethodno pokazane i publikovane [3].

U prvih mesec dana od dijagnoze i početka lečenja, bolesnici sa AML-om mogu doživeti fatalne komplikacije. Taj period je povezan sa visokim mortalitetom, najčešće kao posledica neke od mogućih brojnih komplikacija lečenja [4]. Rana smrt, odnosno smrt u aplaziji (engl. *treatment-related mortality – TRM*) je dobro poznata komplikacija lečenja bolesnika sa AML-om. Definisana je kao smrt koja se javlja unutar 28 dana od otpočinjanja indukcione hemioterapije [4]. Kao najčešći uzroci rane smrti navedeni su infekcija i krvarenje povezani sa citopenijom, međutim u najvećem broju slučajeva je teško, na osnovu kliničkih pokazatelja, predvideti i odrediti uzrok.

Brojne studije pokušale su da ukažu na prognostičke faktore rizika koji se mogu povezati sa pojavom rane smrti kod bolesnika sa AML-om [5]. Iako su ranije studije ukazale na to da je rana smrt češća kod bolesnika starijeg životnog doba, pokazano je da je opšte funkcionalno stanje procenjeno ECOG skalom (engl. *Eastern Cooperative Oncology Group performance status*) bliže povezano sa pojavom rane smrti nego godine starosti. Pored godina starosti i ECOG skora, i neki drugi faktori, kao što su: broj leukocita i trombocita, vrednosti fibrinogena, hemoglobina i laktat dehidrogenaze (LDH), kao i komorbiditetni indeks HCT-CI (engl. *hematopoietic cell transplantation comorbidity index*), mogu uticati na pojavu rane smrti [6].

Ciljevi rada bili su da se odrede kliničke karakteristike bolesnika, prognostički faktori rizika za ranu smrt, učestalost rane smrti, kao i najčešći uzroci rane smrti kod bolesnika sa AML-om, koji su, u periodu od januara 2016. do decembra 2019. godine, lečeni na Klinici za hematologiju Kliničkog centra Srbije.

MATERIJALI I METODE

Istraživanje je sprovedeno u vidu retrospektivne studije, na osnovu baze podataka Klinike za hematologiju Kliničkog Centra Srbije. Istraživanje je uključilo 248 bolesnika sa AML-om, kod kojih je bolest dijagnostikivana i koji su lečeni u periodu od januara 2016. do decembra 2019. godine. Dijagnoza bolesti je postavljena na osnovu: kliničke slike, nalaza u perifernoj krvi i koštanoj srži, kriterijuma FAB klasifikacije (engl. *French–American–*

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogenous clonal malignant disease of the hematopoietic tissue wherein immature hematopoietic cells proliferate and accumulate in the bone marrow, peripheral blood, and other tissues [1].

AML is a rare malignant disease of hematopoietic tissue, which mostly develops in patients of older age [2]. It belongs to a group of diseases with clearly defined cytogenetic and immunological characteristics, which have previously been published elsewhere [3].

Within the first month of diagnosis and treatment initiation, AML patients may suffer fatal complications. This period is connected with high mortality, most frequently as the result of one of many possible treatment complications [4]. Early death, death in aplasia, i.e., treatment-related mortality (TRM) is a well-known treatment complication in AML patients. It is defined as death occurring within 28 days of the initiation of induction chemotherapy [4]. Infection and hemorrhage connected to cytopenia have been stated as the most frequent causes, however, in most cases it is difficult to predict and determine the cause, based on clinical indicators.

Numerous studies have attempted to determine the prognostic risk factors which could be linked to the occurrence of early death in AML patients [5]. Although previous studies have shown that early death occurs more frequently in older patients, it has also been demonstrated that the Eastern Cooperative Oncology Group (ECOG) performance status is more closely linked to the occurrence of early death than age. In addition to age and the ECOG score, other factors, such as: leukocyte count, platelet count, fibrinogen value, hemoglobin level, lactate dehydrogenase (LDH) level, as well as the hematopoietic cell transplantation comorbidity index (HCT-CI), may impact the occurrence of early death [6].

The goals of this paper were to determine the clinical characteristics of patients, prognostic risk factors for early death, the frequency of early death, as well as the most frequent causes of early death in AML patients, who were treated at the Clinic for Hematology of the Clinical Center of Serbia, between January 2016 and December 2019.

MATERIALS AND METHODS

The research was conducted in the form of a retrospective study, based on the database of the Clinic for Hematology of the Clinical Center of Serbia. The study included 248 AML patients, in whom the disease was diagnosed and who were treated in the period January 2016 – December 2019. The diagnosis of AML was established on the basis of the following: clinical presentation, results of the analysis of peripheral blood

British classification), kao i na osnovu preporuka Svetske Zdravstvene Organizacije (SZO) [7,8]. Naša studijska grupa, pored de novo bolesnika sa AML-om, obuhvatila je i 16 (7%) bolesnika koji su prethodno imali druge hematološke bolesti (mijelodisplastični sindrom i mijeloproliferativne bolesti).

Pri dijagnozi, kod bolesnika su evidentirane demografske i kliničko-laboratorijske karakteristike: pol, starost, opšte funkcionalno stanje prema ECOG skali [9], kompletna krvna slika (hemoglobin, broj leukocita, broj trombocita, leukocitarna formula), nivo serumske laktat dehidrogeneze (koji je posebno važno meriti kod hematoloških maligniteta i solidnih tumora) [10], procenat blasta u perifernoj krvi i koštanoj srži, fibrinogen, protrombinsko vreme (engl. *prothrombin time – PT*), aktivirano parcijalno tromboplastinsko vreme (engl. *activated partial thromboplastin time – aPTT*), D-dimer, kao i indeks telesne mase (engl. *body mass index – BMI*). Procena komorbiditeta je vršena na osnovu komorbiditetnog indeksa (engl. *hematopoietic cell transplantation comorbidity index – HCT- CI*), koji se koristi pri transplantaciji matičnih ćelija hematopoeze [11]. Skor diseminovane intravaskularne koagulacije (DIK skor) određivan je prema preporukama Međunarodnog udruženja za trombozu i hemostazu (engl. *International Society on Thrombosis and Hemostasis - ISTH*) [12]. Citogenetski stepen rizika određivan je prema preporukama Evropske grupe za leukemije (engl. *European Leukemia Net – ELN*) [13].

Svi bolesnici starosti ≤ 60 godina lečeni su standardnom „3+7" indukcionom hemioterapijom (HT), u sastavu: daunorubicin, u dozi od 60 mg/m^2, na dan (D) 1, 2, 3, u kombinaciji sa citarabinom u dozi od 200 mg/m^2 dnevno, kontinuirano intravenskom infuzijom, 7 dana. Bolesnici starosti > 60 godina lečeni su, u zavisnosti od ECOG skora i HCT-CI indeksa, HT-om redukovanog intenziteta. Bolesnici koji su imali ECOG ≤ 2 i HCT-CI <3, primali su HT po šemi „3+7 light", u sastavu: daunorubicin, u dozi 45 mg/m^2, na dan 1, 2, 3, u kombinaciji sa citarabinom, u dozi 100 mg/m^2 dnevno, kontinuirano intravenskom (i.v.) infuzijom, 7 dana; dok su pacijenti koji su imali ECOG >2 i HCT-CI ≥3, lečeni po šemi „2+5", u sastavu: daunorubicin, u dozi 30 mg/m^2, i.v., D1, 3, i citarabin, u dozi 100 mg/m^2, i.v., kontinuirano D 1 – 5. Kod starijih bolesnika koji su imali ECOG >2 i HCT-CI ≥3, koji nisu bili nepovoljnog citogenetskog rizika prema ELN klasifikaciji, primenjivana je sledeća HT: niske doze citarabina (20 mg, s.c., na 12h, D 1 – 10), i monoterapija vepezidom, amp. 100 mg, D 1 – 5. Palijativna terapija se sastojala iz primene citoreduktivne terapije (litalir, purinetol) i suportivne terapije, koja je primenjivana kod bolesnika koji nisu mogli da tolerišu nikakvu agresivnu antileukemijsku terapiju. Citoreduktivna terapija

and bone marrow, the French–American–British (FAB) classification criteria, as well as on the basis of the World Health Organization (WHO) recommendations [7,8]. In addition to patients with de novo AML, our study group also included 16 (7%) patients who had previously had other hematological diseases (myelodysplastic syndrome and myeloproliferative diseases).

At diagnosis, the following demographic, clinical, and laboratory characteristics of the patients were recorded: sex, age, ECOG performance status [9], complete blood count (hemoglobin, white blood cell count, thrombocyte count, WBC differential), level of lactate dehydrogenase in the blood (which is especially important to be measured in hematological malignancies and solid tumors) [10], percentage of blasts in peripheral blood and in bone marrow, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer, as well as the body mass index (BMI). The assessment of comorbidities was performed on the basis of the hematopoietic cell transplantation comorbidity index (HCT- CI), which is used in hematopoietic stem cell transplantation [11]. The disseminated intravascular coagulation score (DIC score) was determined according to the recommendations of the International Society on Thrombosis and Hemostasis (ISTH) [12]. The cytogenetic risk level was determined in keeping with the recommendations of European Leukemia Net (ELN) [13].

All patients aged ≤ 60 years were treated with the standard '3+7' induction chemotherapy (CT) consisting of the following: daunorubicin, at a dose of 60 mg/m^2, on days (D) 1, 2 and 3, combined with cytarabine, at a dose of 200 mg/m^2 per day, continuously through intravenous infusion, for a period of 7 days. Patients aged > 60 years were treated, depending on the ECOG score and the HCT-CI index, with reduced intensity CT. Patients with an ECOG ≤ 2 and an HCT-CI <3, received CT according to the '3+7 light' regimen, consisting of the following: daunorubicin, at a dose of 45 mg/m^2, on days 1, 2 and 3, combined with cytarabine, at a dose of 100 mg/m^2 per day, continuously, through intravenous (IV) infusion, for a period of 7 days; while patients with an ECOG >2 and an HCT-CI ≥3, were treated according to the '2+5' regimen, consisting of the following: daunorubicin, at a dose of 30 mg/m^2, IV, D1, 3, and cytarabine, at a dose of 100 mg/m^2, IV, continuously, D 1 – 5. In older patients with an ECOG >2 and an HCT-CI ≥3, who did not have an adverse cytogenetic risk according to the ELN classification, the following CT was administered: low doses of cytarabine (20 mg, SQ, per 12h, D 1 – 10), and monotherapy with vepesid, amp. 100 mg, D 1 – 5. Palliative treatment consisted of the administration of cytoreductive therapy (litalir, purinethol) and supportive treatment, applied in patients who could not

je primenjivana kod bolesnika koji su imali veliki broj leukocita, u cilju smanjena tumorske mase. Rana smrt je definisana kao smrt u toku 28 dana od otpočinjanja indukcione hemioterapije [4].

Za prikupljanje podataka korišćene su otpusne liste uzete iz registara Klinike za hematologiju Kliničkog centra Srbije. Podaci su prikazani deskriptivnim metodama: medijana (minimum- maksimum), apsolutni i relativni brojevi. Za testiranje značajnosti razlike između ispitivanih grupa korišćeni su Man-Vitnijev U test i hi-kvadrat test. Kriterijum za statističku značajnost je bio $p < 0,05$. Za statističku obradu podataka korišćen je softverski program SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA).

REZULTATI

Ispitivanjem je obuhvaćeno 248 odraslih bolesnika sa akutnom mijeloidnom leukemijom, kojima je bolest dijagnostikovana i lečena na Klinici za hematologiju Kliničkog centra Srbije, u periodu od 2016. do 2019. godine. Studijsku grupu činilo je 129 (52%) muškaraca i 119 (48%) žena. Prosečna starost iznosila je 54 godine (opseg: 18 - 81). U starosnoj grupi od 18 - 39 godina, bilo je 46 (18,5%) bolesnika; u starosnoj grupi od 40 - 54 godine, bilo je 64 (25,8%) bolesnika; u grupi starosti od 55 – 64 godine, bilo je 76 bolesnika (30,6%); dok je bilo 62 (25%) pacijenta starija od 65 godina.

Pri dijagnozi, 164 (67,8%) bolesnika je bio dobrog opšteg funkcionalnog stanja – ECOG skor < 2, dok je 78 (32,2%) bolesnika imalo ECOG skor ≥ 2.

Visok HCT-CI indeks (HCT-CI ≥ 3) pri dijagnozi imao je 51 (21,3%) bolesnik, dok je 189 (78,8%) bolesnika imalo HCT-CI < 3.

Bolesnika sa brojem leukocita < 30 x 10^9/l bilo je 159 (64,9%), dok je bolesnika sa brojem leukocita ≥ 30 x 10^9/l bilo 86 (35,1%).

Prema vrednostima LDH u serumu, pacijenti su klasifikovani u grupu sa vrednostima < 450 U/l, kojih je bilo 95 (42,2%), i vrednostima ≥ 450 U/l, kojih je bilo 130 (57,8%).

Prema indeksu telesne mase (BMI), gojaznih bolesnika sa BMI ≥ 30 je bilo 50 (32,7%), dok je bolesnika sa BMI < 30 bilo 103 (67,3%).

Bolesnika sa de novo AML-om bilo je 232 (93,5%), dok je sekundarnih AML-a bilo 16 (6,5%). Od de novo AML-a, prema klasifikaciji AML-a Svetske zdravstvene organizacije, neklasifikovanih AML-a je bilo 221 (95%), bolesnika sa AML-om sa znacima mijelodisplazije je bilo 5 (2%), dok je AML-a nastalih posle prethodnog lečenja (engl. *therapy-related AML – t-AML*) bilo 6 (2,5%).

Prema FAB klasifikaciji AML-a, najveći broj bolesnika je pripadao M4 podtipu – 75 (34%) bolesnika, zatim M2 podtipu – 57 (26%) pacijenata, potom podtipu

tolerate any kind of aggressive antileukemic therapy. Cytoreductive therapy was applied in patients who had a high WBC count, for the purpose of reducing the tumor mass. Early death was defined as death within 28 days of the initiation of induction chemotherapy [4].

Data was collected from the discharge summaries taken from the registers of the Clinic of Hematology of the Clinical Center of Serbia. Data was presented with descriptive measures: the median (minimum – maximum), absolute and relative numbers. The significance of the difference between the study groups was tested with the Mann-Whitney U test and the chi-squared test. The criterion for statistical significance was $p < 0.05$. The software program SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) was used for statistical data processing.

RESULTS

The study included 248 adult patients suffering from acute myeloid leukemia, who were diagnosed with the disease and treated at the Clinic for Hematology of the Clinical Center of Serbia, between 2016 and 2019. The study group was composed of 129 (52%) men and 119 (48%) women. The average age of the patients was 54 years (range: 18 - 81). In the 18 – 39 age group, there were 46 (18.5%) patients; in the 40 - 54 age group, there were 64 (25.8%) patients; in the 55 – 64 age group, there were 76 (30.6%) patients; while there were 62 (25%) patients in the age group 65 years and above.

On diagnosis, 164 (67.8%) patients had a good performance status – ECOG score < 2, while 78 (32.2%) patients had an ECOG score ≥ 2.

A high HCT-CI index (HCT-CI ≥ 3) on diagnosis was found in 51 (21.3%) patients, while 189 (78.8%) patients had an HCT-CI < 3.

There were 159 (64.9%) patients with a WBC count < 30 x 10^9/l, while there were 86 (35.1%) patients with a WBC count ≥ 30 x 10^9/l.

According to the LDH level in the blood, patients were classified into the group with LDH levels < 450 U/l, which included 95 (42.2%) patients, and the group with LDH levels ≥ 450 U/l, which included 130 (57.8%) patients.

According to the body mass index (BMI), there were 50 (32.7%) obese patients with a BMI ≥ 30, while there were 103 (67.3%) patients with a BMI < 30.

There were 232 (93.5%) patients with de novo AML, while there were 16 (6.5%) patients with secondary AML. Of the de novo AML cases, according to the WHO classification of AMLs, there were 221 (95%) unclassified AML patients, 5 (2%) AML patients with signs of myelodysplasia, while there were 6 (2.5%) cases of AML developing after previous treatment, i.e., therapy-related AML (t-AML).

According to the FAB classification of AMLs, the greatest number of patients belonged to the M4 subtype – 75

M5 – 46 (21,5%) bolesnika, i podtipu M1 – 24 (10%) pacijenta. Najmanji broj bolesnika pripadao je M0 podtipu – 19 (8,5%) pacijenata.

Prema ELN citogenetsko-molekularnoj klasifikaciji stepena rizika, najviše bolesnika je bilo sa intermedijarnim rizikom – 157 (65,1%) pacijenata, dok je 11 (4,6%) pacijenata bilo sa povoljnim, a 73 sa (30,3%) nepovoljnim rizikom.

Od 248 bolesnika u studiji, 125 (50,4%) pacijenata je lečeno intenzivnom hemioterapijom, 95 (38,3%) bolesnika je lečeno redukcionom hemioterapijom, dok je 28 (11,3%) pacijenata lečeno palijativnom hemioterapijom.

Rana smrt je nastupila kod 53 (21,4%) bolesnika u studijskoj grupi. Među bolesnicima koji su lečeni intenzivnom hemioterapijom, rana smrt je nastupila kod 23 (18,4%) pacijenta. Rana smrt je nastupila kod 17 (17,9%) bolesnika koji su lečeni redukcionom terapijom. U grupi pacijenata koji su lečeni palijativnom terapijom, rana smrt je nastupila kod 13 (46,3%) bolesnika.

Najveći broj bolesnika u našoj studiji doživeo je indukcionu smrt nakon primene palijativne terapije (46,3%). Kod 6 bolesnika je primenjena citoreduktivna terapija u cilju smanjenja tumorske mase, dok je kod drugih bolesnika, koji su lečeni palijacijom, primenjena citoreduktivna terapija, pošto zbog drugih kliničkih karakteristika (godine starosti, komorbiditeti, i sl.) nisu bili kandidati za primenu indukcione terapije.

Kod 53 (21,4%) bolesnika koji su umrli ranom smrću, prosečna starost je iznosila 56,56 godina (opseg: 18 – 71 godina). U starosnoj grupi od 18 – 39 godina, rana smrt je nastupila kod 4 bolesnika (7,5%); u starosnoj grupi od 40 – 54 godine, nastupila je kod 14 (26,4%) pacijenata; u grupi starosti od 55 – 64 godine, rana smrt je nastupila kod 20 (37,7%) pacijenata; dok je u grupi bolesnika starijih od 65 godina, rana smrt nastupila kod 15 (28,3%) bolesnika.

Klinički parametri koji su ispitivani kao prognostički faktori rizika za ranu smrt prikazani su u Tabeli 1.

Univarijantna analiza pokazala je značajne prognostičke faktore rizika za ranu smrt kod bolesnika sa AML-om, a to su: godine starosti, ECOG skor, broj leukocita, vrednost LDH, procenat blasta u perifernoj krvi i koštanoj srži, vrednost PT, kao i ISTH skor. Godine starosti pokazale su se kao značajan prognostički faktor rizika za ranu smrt, jer je prosečna starost bolesnika kod kojih je nastupila rana smrt bila 56,56 godina ($p = 0,047$). Bolesnici koji su imali ECOG PS ≥ 2, imali su statistički veće šanse da kod njih nastupi smrt u indukciji u odnosu na bolesnike koji su imali ECOG PS < 2 ($p = 0,001$). Takođe, bolesnici sa brojem leukocita ≥ 30 x 10^9/l su imali veću šansu da dožive indukcionu smrt u odnosu na bolesnike sa brojem leukocita < 30 x 10^9/l ($p = 0,022$). Serumska vrednost LDH ≥ 450 U/l se takođe pokazala

(34%) patients, followed by the M2 subtype – 57 (26%) patients, the M5 subtype – 46 (21.5%) patients, and the M1 subtype – 24 (10%) patients. The smallest number of patients belonged to the M0 subtype – 19 (8.5%) patients.

According to ELN cytogenetic and molecular risk stratification, the greatest number of patients had intermediate risk – 157 (65.1%) patients, while 11 (4.6%) patients had favorable risk, and 73 (30.3%) patients had adverse risk.

Of the 248 patients included in the study, 125 (50.4%) patients were treated with chemotherapy, 95 (38.3%) patients were treated with reduction chemotherapy, while 28 (11.3%) patients were treated with palliative chemotherapy.

Early death occurred in 53 (21.4%) patients within the study group. Among the patients treated with intensive chemotherapy, early death occurred in 23 (18.4%) cases. Early death occurred in 17 (17.9%) patients treated with reduction therapy. In the group of patients treated with palliative therapy, early death occurred in 13 (46.3%) patients.

The greatest number of patients in our study suffered induction death after the administration of palliative therapy (46.3%). Cytoreductive therapy was applied in 6 patients, with the aim of reducing the tumor mass, while in other patients treated with palliative treatment, cytoreductive therapy was administered due to the fact that these patients were not candidates for the application of induction therapy, owing to other clinical characteristics (age, comorbidities, etc.).

In 53 (21.4%) patients who suffered early death, the average age was 56.56 years (range: 18 – 71 years). In the 18 – 39 age group, early death occurred in 4 (7.5%) patients; in the 40 – 54 age group, early death occurred in 14 (26.4%) patients; in the 55 – 64 age group, early death occurred in 20 (37.7%) patients; while in the group of patients aged over 65, early death occurred in 15 (28.3%) patients.

The clinical parameters that were studied as prognostic risk factors for early death are presented in Table1.

Univariate analysis showed the following significant prognostic risk factors for early death in AML patients: age, the ECOG score, the WBC count, the LDH level, the percentage of blasts in peripheral blood, the percentage of blasts in bone marrow, the PT value, and the ISTH score. Age proved to be a significant prognostic risk factor for early death, as the average age of the patients in whom early death occurred was 56.56 years ($p = 0.047$). There was a statistically higher probability of induction death occurring in patients who had an ECOG PS ≥ 2, than in patients with an ECOG PS < 2 ($p = 0.001$). Also, patients with a WBC count ≥ 30 x 10^9/l had a higher probability of suffering induction death as compared

Tabela 1. Prognostički faktori rizika za ranu smrt

Table 1. Prognostic risk factors for early death

Karakteristike / *Characteristics*	**RS / *ED***	**Bez RS / *Without ED***	**p**
Starost (godine, prosečna starost) / *Age (years, average age)*	56.6	52.9	0.047
Pol, *n* (%) / *Sex, n* (%)			
Muški / *Male*	25 (47.2%)	104 (53.3%)	0.261
Ženski / *Female*	28 (52.8%)	91 (46.7%)	
ECOG, *n* (%) ≥2 / *ECOG ≥2, n* (%)	26 (53.1%)	52 (26.9%)	0.001
HCT-CI ≥3, *n* (%) / *HCT-CI ≥3, n* (%)	10 (20.4%)	41 (21.5%)	0.523
Le (x10^9/l), medijana (opseg) / *Le (x10^9/l), median (range)*	24.9 (1 – 473)	9.8 (0 – 349)	0.176
Le ≥ 30 (x10^9/l), *n (%) / Le ≥ 30 (x10^9/l), n (%)*	25 (48.1%)	61 (31.6%)	0.022
Hb, medijana (opseg) / *Hb, median (range)*	98 (22 – 134)	95 (44 – 221)	0.473
Tr (x10^9/l), medijana (opseg) / *Plt (x10^9/l), median (range)*	47 l (1 – 244)	49 (1 – 421)	0.814
LDH ≥ 450 (U/l), *n* (%) / *LDH ≥ 450 (U/l), n (%)*	108 (61.4%)	22 (44.9%)	0.029
Blasti u PK (%), medijana (opseg) / *Blasts in PB (%), median (range)*	39 (0 – 98)	16 (0 – 99)	0.005
Blasti u KS (%), medijana (opseg) / *Blasts in BM (%), median (range)*	70 (18 – 94)	60 (1 – 96)	0.003
BMI ≥ 30.0, *n* (%) / *BMI ≥ 30.0, n* (%)	11 (35.5%)	39 (32%)	0.431
PT, medijana (opseg) / *PT, median (range)*	63 (37 – 100)	75 (83 – 114)	<0.001
PTT, medijana (opseg) / *PTT, median (range)*	29.9 (20 – 39)	28.4 (20 – 51)	0.113
Fibrinogen (g/l), medijana (opseg) / *Fibrinogen (g/l), median (range)*	5.42 (2 – 10)	5.10 (1 – 11)	0.763
ISTH skor, medijana (opseg) / *ISTH score, median (range)*	4 (0 – 7)	3 (0 – 7)	0.018
ELN, *n* (%) / *ELN, n* (%)			
Povoljan / *Favorable*	2 (4.3%)	9 (4.6%)	0.894
Intermedijarni / *Intermediate*	32 (68.1%)	125 (64.4%)	
Nepovoljan / *Adverse*	13 (27.7 %)	60 (30.9%)	

RS – rana smrt; n – broj (engl. *number*); *ECOG* – (engl. *Eastern Cooperative Oncology Group*); *HCT-CI* (engl. *hematopoietic cell transplantation comorbidity index*); Le – leukociti; Hb – hemoglobin; Tr – trombociti; PK – periferna krv; KS – koštana srž; *BMI* – indeks telesne mase (engl. *body mass index*); *PT* – protrombinsko vreme (engl. *prothrombin time*); *PTT* – parcijalno tromboplastinsko vreme (engl. *partial thromboplastin time*); *ISTH* (engl. *International Society on Thrombosis and Hemostasis*); Međunarodne radne grupe za leukemiju - *European Leukemia Net (ELN)*

ED – early death; n – number; ECOG – Eastern Cooperative Oncology Group; HCT-CI – hematopoietic cell transplantation comorbidity index; Le – leukocytes; Hb – hemoglobin; Plt – platelets; PB – peripheral blood; BM – bone marrow; BMI – body mass index ; PT – prothrombin time; PTT – partial thromboplastin time; ISTH – International Society on Thrombosis and Hemostasis of the European Leukemia Net (ELN)

kao prognostički faktor rizika za ranu smrt u odnosu na LDH < 450 U/l (p = 0,029). Procenat blasta u perifernoj krvi (p = 0,005), kao i procenat blasta u koštanoj srži (p = 0,003), pokazani su kao statistički značajni prognostički faktori rizika za ranu smrti.

Vrednost PT-a se takođe pokazala kao prognostički faktor rizika (p < 0,001). Kao prognostički faktor rizika za ranu smrt pokazan je i ISTH skor (p = 0,018) (Tabela 1).

to patients with a WBC count < 30 x 10^9/l (p = 0.022). The LDH blood level ≥ 450 U/l was also shown to be a prognostic risk factor for early death, as compared to LDH < 450 U/l (p = 0.029). The percentage of blasts in peripheral blood (p = 0.005), as well as the percentage of blasts in bone marrow (p = 0.003), proved to be statistically significant prognostic risk factors for early death.

Tabela 2. Najčešći uzroci rane smrti i njihova zastupljenost u starosnim grupama

Table 2. The most common causes of early death and their prevalence in age groups

	Ukupno / *Total*	18 – 39 godina / *years*	40 – 54 godina / *years*	55 – 64 godina / *years*	> 65 godina / *years*
Sepsa / *Sepsis*	17 (32.1%)	1 (25%)	5 (35.7%)	7 (35%)	4 (26.7%)
Pneumonija / *Pneumonia*	5 (9.4%)	0 (0%)	2 (14.3%)	1 (5%)	2 (13.3%)
CNS hemoragija / *CNS hemorrhage*	7 (13.2%)	0 (0%)	3 (21.4%)	3 (15%)	1 (6.7%)
Respiratorna insuficijencija / *Respiratory failure*	13 (24.5%)	1 (25%)	0 (0%)	6 (30%)	6 (40%)
Srčana insuficijencija / *Heart failure*	3 (5.7%)	1 (25%)	1 (7.1%)	1 (5%)	0 (0%)
Enterokolitis / *Enterocolitis*	4 (7.5%)	1 (25%)	1 (7.1%)	1 (5%)	1 (6.7%)
GIT hemoragija / *GIT hemorrhage*	1 (1.9%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)
ABI / *ARF*	3 (5.7%)	0 (0%)	1 (7.1%)	1 (5%)	1 (6.7%)

CNS – centralni nervni sistem; GIT – gastrointestinalni trakt; ABI - akutna bubrežna insuficijencija

CNS – central nervous system; GIT – gastrointestinal tract; ARF – acute renal failure

Analiza uticaja ostalih ispitivanih parametara, kao prognostičkih faktora rizika za ranu smrt, nije pokazala statistički značajne rezultate (Tabela 1). Od 53 umrla bolesnika, rana smrt je najčešće nastupila kao posledica sepse – kod 17 (32,1%) bolesnika; respiratorne insuficijencije – kod 13 (24,5%) pacijenata; krvarenja u CNS-u – kod 7 (13,2%) pacijenata; pneumonije – kod 5 (9,4%) bolesnika; enterokolitisa – kod 4 (7,5%) pacijenta; srčane insuficijencije – kod 3 (6,7%) bolesnika; akutne bubrežne insuficijencije – kod 3 (6,7%) pacijenta; dok je kod jednog (1,9%) pacijenta, rana smrt nastupila kao posledica krvarenja u GIT-u (Tabela 2).

Najčešći uzrok rane smrti kod bolesnika starosnog doba od 40 – 65 godina bila je sepsa – kod 12 (35%) bolesnika, dok je kod bolesnika starijih od 65 godina najčešći uzrok rane smrti bila respiratorna insuficijencija – kod 6 (40%) pacijenata.

DISKUSIJA

Rana smrt je dobro poznata komplikacija indukcione hemioterapije primenjene kod bolesnika sa AML-om, te su zbog toga sprovedene brojne studije koje bi ukazale na prognostičke faktore rizika koji do nje dovode [6]. U našoj studiji, pojedine karakteristike bolesnika pokazale su se kao statistički značajni prognostički faktori rizika za ranu smrt.

Rana smrt je nastupila kod 53 bolesnika (21,4%) u našoj studiji. Valter i saradnici navode da je u njihovoj studiji rana smrt nastupila kod 10,4% bolesnika [4].

U našoj studiji, najčešći uzrok rane smrti kod bolesnika starosti od 40 – 65 godina bila je sepsa, dok je kod starijih od 65 godina najčešći uzrok indukcione smrti bila respiratorna insuficijencija. Za razliku od naše studije, u studiji koju su sproveli Ho i saradnici, ukazano je na to da je, u njihovoj studijskoj grupi, rana smrt kod mlađih bolesnika češće bila uzrokovana respiratornom

The PT value also proved to be a prognostic risk factor ($p < 0.001$). The ISTH score ($p = 0.018$) was also shown to be a prognostic risk factor for early death (Table 1).

The analysis of the influence of other analyzed parameters, as prognostic risk factors of early death, did not show statistically significant results (Table 1). Of the 53 deceased patients, early death occurred most frequently as the result of the following: sepsis – in 17 (32.1%) patients; respiratory insufficiency – in 13 (24.5%) patients; CNS hemorrhage – in 7 (13.2%) patients; pneumonia – in 5 (9.4%) patients; enterocolitis – in 4 (7.5%) patients; heart failure – in 3 (6.7%) patients; acute renal insufficiency – in 3 (6.7%) patients; while in one (1.9%) patient, early death occurred as the result of GIT hemorrhage (Table 2).

The most frequent cause of early death in patients aged 40 – 65 years was sepsis – in 12 (35%) patients, while in patients aged over 65 years, the most frequent cause of early death was respiratory insufficiency – in 6 (40%) patients.

DISCUSSION

Early death is a well-known complication of induction chemotherapy applied in AML patients, which is why numerous studies have been carried out so as to indicate prognostic risk factors that lead to early death [6]. In our study, individual patient characteristics proved to be statistically significant prognostic risk factors for early death.

In our study, early death occurred in 53 (21.4%) patients. Walter et al. state that, in their study, early death occurred in 10.4% of patients [4].

In our study, the most frequent cause of early death, in patients aged 40 – 65 years, was sepsis, while in patients older than 65 years, the most common cause of induction death was respiratory insufficiency. As opposed

insuficijencijom, u odnosu na stariju populaciju u ovoj studijskoj grupi. Takođe, u njihovoj studijskoj grupi, sepsa nije svrstana među najčešće uzroke smrti [14].

U našoj studiji, prosečna starost bolesnika u kojoj se desila indukciona smrt iznosila je 56 godina. Naša studija je pokazala da godine spadaju u značajne faktore rizika za ranu smrt ($p = 0,047$). U svojoj studiji, Othus i saradnici takođe navode da su bolesnici u grupi u kojoj je nastupila indukciona smrt bili starijeg životnog doba, sa prosečnom starošću od 66 godina [5]. U svojoj studiji, Ho i saradnici takođe navode da se rana smrt češće javlja kod bolesnika starijeg životnog doba, međutim prosečna starost nije precizirana [14].

ECOG skor je takođe pokazan kao značajan prognostički faktor rizika. Naša studija je takođe pokazala da je u grupi pacijenata koji su imali ECOG PS ≥ 2 postojao veći procenat rane smrti, u odnosu na one bolesnike koji su imali ECOG PS < 2 ($p = 0,001$). U svojoj studiji, Malkan i saradnici ukazuju na to da su bolesnici koji su imali ECOG skor < 2 imali manji procenat rane smrtnosti, u odnosu na one koji su imali ECOG PS ≥ 2, i navode ga kao najznačajniji nezavisni prognostički faktor rizika za ranu smrt [15].

Kod bolesnika u našoj studiji, povišene vrednosti LDH (LDH ≥ 450 U/l) pokazale su se kao značajan prognostički faktor rane smrti ($p = 0,029$). Ovo pokazuje i studija koju su sproveli Djunić i saradnici, gde je univarijantna analiza pokazala da je značajan prognostički faktor rizika za ranu smrt porast serumske LDH [16].

Statistički značajno je pokazan uticaj vrednosti leukocita ≥ 30 x 10^9/l na pojavu rane smrti kod bolesnika u našoj studiji ($p = 0,029$). Studija koju su sproveli Malkan i saradnici takođe je pokazala uticaj povišenih vrednosti leukocita na pojavu rane smrti kod bolesnika sa AML-om [15]. Sa druge strane, Valter i saradnici u svojoj studiji nisu pokazali povišen broj leukocita kao statistički značajan prognostički faktor rizika za ranu smrt [4].

U našoj studiji se pokazalo da su procenat blasta u perifernoj krvi ($p = 0,005$) i procenat blasta u koštanoj srži ($p = 0,003$) statistički značajni prognostički faktori rizika. Studija koju su sproveli Othus i saradnici i studija koju su sproveli Liu i saradnici, takođe su pokazale ova dva parametra kao statistički značajne prognostičke faktore rizika za indukcionu smrt [5,17].

U našoj studiji se vrednost protrombinskog vremena takođe pokazala kao značajan prognostički faktor rizika za ranu smrt ($p < 0,001$). U našoj studiji se ISTH skor ≥ 4 pokazao kao značajan prognostički faktor rizika ($p = 0,018$). Studija koju su sproveli Berger i saradnici ukazala je na značaj ISTH skora ≥ 4 kao prognostičkog faktora [18]. Studija koju su sproveli Liburel i saradnici je takođe potvrdila značaj ova dva

to our study, in a study by Ho et al., it has been indicated that, in their study group, early death in younger patients was more frequently caused by respiratory insufficiency, as compared to the older population in this study group. Also, in their study group, sepsis was not reported amongst the most frequent causes of death [14].

In our study, the average patient age at the time of induction death was 56 years. Our study showed age to be amongst the significant risk factors for early death ($p = 0.047$). In their study, Othus et al. also state that the patients belonging to the group where induction death occurred were older, with an average age of 66 years [5]. In their study, Ho et al. also indicate that early death occurred more frequently in older patients, however, they did not specify the mean age [14].

The average ECOG score also proved to be a significant prognostic risk factor. Our study also showed that there was a higher percentage of early death in the group of patients with an ECOG PS ≥ 2, as compared to the patients with an ECOG PS < 2 ($p = 0.001$). In their study, Malkan et al. indicated that the patients with an ECOG score < 2, had a lesser percentage of early mortality, as compared to those whose score was ECOG PS ≥ 2, and they state it as the most significant independent prognostic risk factor for early death [15].

Elevated LDH levels (LDH ≥ 450 U/l) proved to be a significant prognostic factor of early death in the patients involved in our study ($p = 0.029$). This was also demonstrated by the study carried out by Djunić et al., wherein univariate analysis showed that the rise in the level of LDH in the blood was a significant prognostic risk factor for early death [16].

The statistically significant impact of white blood cell values ≥ 30 x 10^9/l on the occurrence of early death in the patients involved in our study has also been demonstrated ($p = 0,029$). A study by Malkan et al. also showed the influence of elevated leukocyte values on the occurrence of early death in AML patients [15]. On the other hand, in their study, Walter et al. did not report elevated WBC count as a statistically significant prognostic risk factor for early death [4].

In our study, it was shown that that the percentage of blasts in peripheral blood ($p = 0.005$) as well as the percentage of blasts in bone marrow ($p = 0.003$) were statistically significant prognostic risk factors. A study by Othus et al. as well as a study by Liu et al., also identified these two parameters as statistically significant prognostic risk factors for induction death [5,17].

In our study, the value of prothrombin time also proved to be a significant prognostic risk factor for early death ($p < 0.001$). In our study, an ISTH score ≥ 4 proved to be a significant prognostic risk factor ($p = 0.018$). A study by Berger et al. indicated the significance of an

faktora u nastanku trombotičnih epizoda i posledične indukcione smrti [19].

Studija koju su sproveli Djunić i saradnici pokazala je da je HCT-CI ≥ 3 najznačajniji prognostički faktor rizika za ranu smrt [16]. Takođe je i studija koju su sproveli Ho i saradnici pokazala da je HCT-CI ≥ 3 značajan prognostički faktor rizika za ranu smrt [14]. Međutim, u našoj studiji, HCT-CI ≥ 3 nije pokazan kao statistički značajan prognostički faktor rizika za ranu smrt ($p = 0,523$).

ZAKLJUČAK

Naša studija je pokazala da su godine starosti, opšte funkcionalno stanje bolesnika izraženo putem ECOG skora, broj leukocita, vrednost LDH, procenat blasta u perifernoj krvi i koštanoj srži, vrednost PT, kao i ISTH skor, značajni prognostički faktori rizika za ranu smrt kod bolesnika sa akutnom mijeloidnom leukemijom.

Takođe, naša studija je pokazala da je najčešći uzrok rane smrti kod bolesnika starosnog doba od 40 – 65 godina bila sepsa, dok je kod bolesnika starijih od 65 godina to bila respiratorna insuficijencija. U velikom broju slučajeva je teško odrediti uzrok rane smrti na osnovu kliničkih parametara, te je nesigurno oslanjati se na njih. Samim tim, potrebna su dalja istraživanja i primena novih dijagnostičkih metoda, koje bi pomogle u individualnoj proceni stanja bolesnika i eventualnoj predikciji i prevenciji rane smrti.

Sukob interesa: Nije prijavljen.

ISTH score ≥ 4 as a prognostic factor [18]. A study by Libourel et al. also confirmed the significance of these two factors in the development of thrombotic episodes, and consequent induction death [19].

A study by Djunić et al. showed HCT-CI ≥ 3 to be the most significant prognostic risk factor for early death [16]. Also, a study by Ho et al showed HCT-CI ≥ 3 to be a significant prognostic risk factor for early death [14]. However, in our study, HCT-CI ≥ 3 did not prove to be a statistically significant prognostic risk factor for early death ($p = 0.523$).

CONCLUSION

Our study has shown age, performance status of the patient expressed as the ECOG score, WBC count, LDH level, percentage of blasts in peripheral blood, percentage of blasts in bone marrow, PT value, as well as the ISTH score, to be significant prognostic risk factors for early death in patients with acute myeloid leukemia.

Also, our study has shown the most frequent cause of early death in patients aged 40 – 65 years to be sepsis, while in patients older than 65 years, this has proven to be respiratory insufficiency. In a great number of the cases, it is difficult to determine the cause of early death, based on clinical parameters, which is why these cannot be taken as definitive indicators. Therefore, further research is necessary as well as the application of new diagnostic methods, which would help in the individual assessment of the patient's status and in the possible prediction and prevention of early death.

Conflict of interest: None declared.

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