Starija životna dob u hrvatskoj kliničkoj praksi nije diskriminirajući čimbenik za transplantaciju jetre

/ *Older Age in Croatian Clinical Practice is not Discriminative Factor for Liver Transplantation*

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Transplantacija jetre je oblik terapije kod ireverzibilnog akutnog ili kroničnog zatajenja jetre. Bolje liječenje brojnih bolesti rezultiralo je produženjem životnog vijeka s posljedičnim starenjem populacije. Valja naglasiti da ne postoji dobna granica kako za primatelja tako ni za davatelja organa kod transplantacijskog liječenja, pa se sve češće radi o starijim primateljima/davateljima organa. Cilj ovog rada je utvrditi udio bolesnika starijih od 65 godina liječenih transplantacijom jetre u ukupnom broju jednako liječenih bolesnika, te prikazati vrstu i učestalost komplikacija ovakvog liječenja. Od 1. siječnja 2013 do 1. rujna 2019. godine u KB Merkur transplantacijom jetre liječeno je ukupno 746 bolesnika od kojih je 206 (27,6 %) bilo starije od 65 godina. U toj podskupini bolesnika najčešća indikacija za transplantaciju jetre bila je primarna neoplazma jetre (44,2 %), potom alkoholna bolest jetre (29,6 %), dok su ostale indikacije bile prisutne u 26,2 % bolesnika. Mortalitet tijekom zahvata ili u posttransplantacijskom praćenju u ovoj podskupini bolesnika iznosio je 31 %. Najčešći uzroci smrti bile su: infekcije, sepsa i multiorgansko zatajenje. Kao zaključak može se reći da životna dob bolesnika nije kontraindikacija za transplantacijsko liječenje, osobito kod bolesnika kojima je to jedina metoda liječenja bolesti u vitalnoj indikaciji. Psihijatrijska procjena je važan i sastavni dio pre- i posttransplantacijske faze praćenja bolesnika.

/ Background: Liver transplantation is a method of treatment for irreversible end-stage liver insufficiency. Improved treatment of various diseases has led to the extension of life expectancy and consequently older world population. It must be pointed out that there is no age limit either for organ donation or organ transplantation. Since the population is getting older, today more and more patients who receive liver transplantation are elderly patients. The aim of this study was to show the percentage of elderly patients who received liver transplantation in our centre, as well as to analyse the rate and type of complications of the treatment. The study was retrospective, and included patients treated by liver transplantation in the period between January 1, 2013 and September 1, 2019 at the University Hospital Merkur. There were 746 treated patients, 206 of whom (27.6%) were elderly (>65 years) patients. The main indication for the treatment was primary liver neoplasm (44.2%), followed by alcohol liver disease (29.6%), and other indications (26.2%). The mortality rate during operation and in the post-transplantation follow up period was 31%. The most frequent cause of death were infections, sepsis, and multiorgan failure. Conclusion: Older age is not a contraindication for liver transplantation, especially if it is a lifesaving procedure. Psychiatric assessment is an important and integral part of the pre- and post-transplantation follow-up phase.

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UVOD

Prvu transplantaciju jetre učinio je Thomas Starzl 1963. godine. Od tada pa do danas svake godine povećava se broj transplantacija jetre, jednim dijelom zbog sve većeg broja indikacija za takvo liječenje, a sigurno i zbog većeg broja bolesnika koji su pogodni za ovakav izbor liječenja (1). U liječenje transplantacijom jetre, uz sam kirurški zahvat presađivanja organa, spadaju i procjena potrebe za takvim liječenjem, potvrda o provedenim iscrpnim mjerama konzervativnog liječenja, kao i detaljna klinička tjelesna i psihijatrijska obrada svakog potencijalnog kandidata u samom transplantacijskom centru (2).

U našem transplantacijskom centru posljednjih se godina obavi u prosjeku preko 100 transplantacija jetre godišnje. Rastom broja transplantacija sve češće se radi o primateljima organa koji su stariji od 65 godina (u daljem tekstu "u starijoj životnoj dobi"). Unatoč svim napretcima u liječenju komplikacije transplantacijskog liječenja ipak su češće u bolesnika starije životne dobi nego u mlađih, neovisno o bolesti koja je uzrokovala zatajenje jetre (3).

Treba imati na umu da je istodobno sve starija i dob davatelja organa o čemu posebno treba voditi računa prigodom alokacije organa (4). Pažljivim probirom starijih bolesnika danas je korist transplantacije jetre jednaka kako kod mlađih tako i kod starijih bolesnika (5).

INTRODUCTION

The first liver transplantation was performed by Thomas Starzl in 1963. Since then, the number of liver transplantations has been steadily rising, at least in part due to the expanding field of indications for such treatment (1). More and more patients suffering from end-stage liver insufficiency can be stabilized by medicamentous therapy enough to be suitable candidates for transplantation. Apart from the operation/transplantation itself, there are several important steps within the transplantation process, for example physical and psychiatric evaluation of the patient, indication for transplantation, evidence that conservative measures were applied but without beneficial effect, diagnostic evaluation of the patient in a transplantation centre, etc. (2).

On average, one hundred liver transplantations are performed in our centre per year. With a rise in the number of procedures, as well as with improved selection of the patients and preoperative assessment and treatment of these patients, more and more elderly patients (defined as older than 65 years) are treated by transplantation. Even with all these improvements they still have a higher rate of complications related to transplantation treatment than younger patients, regardless of the disease that caused liver insufficiency (3).

At the same time, donors are also older than before, which should be specifically taken into

U Kliničkoj bolnici Merkur jedini kriterij za transplantacijsko liječenje je težina jetrene bolesti, a danas najčešća indikacija za transplantaciju jetre je primarna neoplazma jetre (hepatocelularni karcinom), potom slijedi alkoholna bolest jetre, te dalje autoimune bolesti, virusne bolesti (hepatitis B i C), sekundarna bilijarna ciroza, policistična bolest, Budd Chiarijev sindrom i dr. (6).

Poboljšanjem probira bolesnika, boljim mogućnostima medikamentne terapije i usavršavanjem tehnike transplantacije došlo je do smanjenja pojave postoperacijskih komplikacija, a time je i život bolesnika nakon transplantacije jetre postao kvalitetniji (7). Pri tom se ne smije zaboraviti da bolesnici dolaze u naš centar obično u teškom općem stanju s prisutnim brojnim komplikacijama dekompenzirane ciroze jetre. Ako periproceduralni tijek prođe uredno, čak i kod takvih bolesnika, dolazi do značajnog fizičkog i psihičkog poboljšanja i ozdravljenja.

Kod većine bolesnika nakon transplantacije jetre dolazi do značajnog porasta tjelesne težine, što se ranije smatralo pozitivnim pokazateljem. Međutim, danas se zna da takvo dobivanje na tjelesnoj težini tijekom dužeg vremena nosi bolesniku više rizika nego koristi (8).

Transplantacijska medicina je multidisciplinska struka u kojoj zajednički rade liječnici različitih specijalnosti (kirurzi, internisti, psihijatri, anesteziolozi, radiolozi, patolozi, mikrobiolozi, transfuziolozi), medicinski tehničari, medicinske sestre instrumentarke i ostali. Psihijatrijska potpora ključna je u bolesnikovom prihvaćanju vlastite bolesti, činjenice da je presađivanje organa neophodno, kao i u bržem oporavku nakon transplantacije. Važno je da bolesnik u cijeli postupak ulazi s punim povjerenjem s obzirom da se radi o jednom od najsloženijih oblika liječenja danas (9). Stoga je i razgovor s psihijatrom nužan. Na taj način bolesnik bolje shvaća vlastitu bolest i prihvaća transplantaciju kao jedinu metodu liječenja sa svim komplikacijama koje ona nosi (10).

account during allocation of organs (4). With improved selection, especially of older patients, the benefit of liver transplantation is today almost the same for elderly and younger patients (5).

Therefore, in our clinic age itself is not a criterium nor a contraindication for liver transplantation, and the decision is made based on the disease that caused liver failure.

In our facility, the main indication for liver transplantation is primary liver neoplasm (hepatocellular carcinoma), followed by alcohol liver disease, autoimmune liver disease, viral liver diseases (hepatitis B and C), secondary biliary cirrhosis, polycystic disease, Budd Chiari syndrome, and other liver diseases (6).

With improved patient selection, better medicamentous and other preoperative assessment and treatment of the patient, improved operative techniques, postoperative complications have been diminished, while the quality of life after procedure has also been improved (7). It should be mentioned that the patients referred to our centre are often in life-threatening conditions, with numerous complications of advanced liver disease. If we manage to stabilize the patient and if the periprocedural course is good, even such patients usually recover quickly. Weight gain was previously considered a positive sign, but today it is known that weight gain over a longer time period also has negative effects (8).

Transplantation medicine is a multidisciplinary branch in which many different types of doctors (surgeons, internal medicine specialists, psychiatrists, anaesthesiologists, pathologists), nurses, and other medical professionals need to work together. Teamwork is important in all steps of the process, for example during the patient's acceptance of the disease and the fact that organ transplantation is indicated, as well as in the recovery phase after the transplantation. It is of significant help it the patient un-

Kako je jedna od komplikacija uznapredovalog zatajenja jetre hepatalna encefalopatija koja se može manifestirati čitavim nizom psihijatrijskih i neuroloških poremećaja (od minimalnih promjena osobnosti, pospanosti, usporenog govora preko poremećaja kognitivnih funkcija, neuromuskularne neusklađenosti i tremora do sopora i kome) zadaća je psihijatra razlučiti radi li se o anksioznosti, depresiji, halucinacijama i poremećajima ličnosti u sklopu hepatalne encefalopatije ili se pak radi o primarnim psihijatrijskim poremećajima ličnosti, koje pak nisu uzrokovane metaboličkim ili elektrolitskim disbalansom kao posljedica jetrene bolesti (11).

Nakon transplantacije bolesnici trebaju uzimati imunosupresivne lijekove od kojih su danas najznačajniji kalcineurinski inhibitori, kortikosteroidni te mikofenolat-mofetil. Međutim i lijekovi, posebno prve dvije navedene skupine uzrokuju česte psihijatrijsko-neurološke nuspojave, od smetenosti, depresije i smetnji raspoloženja pa do duševnih poremećaja. To je osobito često u bolesnika liječenih kalcineurinskim inhibitorima. Sigurno da je situacija jednostavnija, ako se navedene nuspojave razviju kao odgovor na kortikosteroidnu terapiju jer se ona može reducirati, a potom tijekom 2 - 3 mjeseca i u potpunosti izostaviti iz terapije (12).

Upravo zajedničkim, timskim radom liječenje postaje sigurnije, kvalitetnije, uz mogućnosti prilagodbe liječenja bolesniku, pa je stoga i bolji postotak preživljenja jetrenog presatka i samog primatelja (13).

CILJ ISTRAŽIVANJA

Cilj ovog rada bio je utvrditi udio bolesnika starijih od 65 godina liječenih transplantacijom jetre u ukupnom broju ovako liječenih bolesnika, te prikazati vrstu i učestalost komplikacija ovakvog liječenja.

derstands and is motivated to go through such treatment (9).

Therefore, consultation with a psychiatrist is an integral part of patient selection. There are also other reasons why this is an integral part of the assessment of the patients (10).

Many patients already have portal encephalopathy with different clinical presentations: from minimal personality changes, somnolence, slower speech, cognitive dysfunction, neuromuscular problems such as tremors to the soporous or comatose state. The role of a psychiatrist is to differentiate between anxiety, depression, hallucinations, and personality changes as part of portal encephalopathy and primary psychiatric disease not caused by metabolic or electrolyte disbalance (11).

After transplantation, patients are treated by three different immunosuppressive medications: calcineurin inhibitors, corticosteroids, and mycophenolate mofetil. The first two groups of medications can have significant psychiatric-neurologic side effects (ranging from confusion, depression, and mood changes to serious mental problems), especially calcineurin inhibitors. It is easier if side effects are caused by corticosteroid therapy since this therapy can be reduced and discontinued completely after 2-3 months (12).

Teamwork and a multidisciplinary approach make the treatment safer, better, individualised, with better results of the treatment in terms of lower graft loss rates, as well as lower incidence of side effects of the therapy (13).

STUDY AIM

The aim of this study was to show the percentage of the elderly patients treated by liver transplantation in our centre as well as to analyse the rate and type of complications of the treatment.

METODA ISTRAŽIVANJA

U studiju su uključeni svi bolesnici liječeni kadaveričnom ortotopnom transplantacijom jetre u Kliničkoj bolnici Merkur, Zagreb u razdoblju od 1. siječnja 2013 do 1.rujna 2019. Analiziran je ukupan broj ovako liječenih bolesnika kao i udio bolesnika starijih od 65 godina s osvrtom na indikacije za ovakvo liječenje, učestalost komplikacija osnovne bolesti (tumori, hepatitis C) te postoperacijskih infekcija kao glavnog uzroka smrti.

REZULTATI

Prva transplantacija jetre u Kliničkoj bolnici Merkur učinjena je 1998. godine. Od tada do danas broj je transplantacija u stalnom porastu. To najbolje pokazuje podatak da je između 1998. i 2007. godine učinjeno ukupno oko 200 transplantacija jetre, a od 2011. godine se svake godine učini više od 100 transplantacija jetre. Najveći broj obavljenih zahvata zabilježen je 2015. godine, kada je učinjeno ukupno 130 transplantacija jetre. U analiziranom razdoblju 746 bolesnika liječeno je transplantacijom jetre, od kojih je 206 (27,6 %) bolesnika ili svaki četvrti bolesnik bio stariji od 65 godina. U toj podskupini bolesnika najčešća indikacija za transplantaciju jetre bila je primarna neoplazma jetre - kod 91 (44,2 % bolesnika starije dobi), potom je slijedila alkoholna bolest jetre - kod 61 (29,6 % bolesnika starije dobi), a sve ostale indikacije bile su prisutne u preostala 54 bolesnika (26,2 % bolesnika starije dobi).

Mortalitet tijekom zahvata ili u daljem posttransplantacijskom praćenju u skupini osoba starije životne dobio iznosio je 31 % (odnosno 64 bolesnika su umrla), a najčešći uzroci smrti bile su: kompliciranе infekcije, sepsa i multiorgansko zatajenje.

RASPRAVA

Transplantacija jetre je metoda kojom se sve češće i sve uspješnije liječe bolesnici s ireverzibilnim akutnim ili kroničnim zatajenjem jetre

METHODS

The study included patients treated by cadaveric orthotopic liver transplantation in Clinical Hospital Merkur Zagreb in the period between January 1, 2013 and September 1, 2019. The number of patients treated by liver transplantation, the percentage of elderly patient, as well as the analysis of indications for such treatment and the rate of complications of the main disease (tumour, hepatitis C) and postoperative infections as the main cause of death were analysed.

RESULTS

The first liver transplantation in Clinical Hospital Merkur was performed in 1998. Since then, the number of procedures per year has been steadily rising. Between 1998 and 2007 altogether 200 liver transplantations were performed, while for the last 8 years more than 100 liver transplantations a year have been performed. The most liver transplantations were performed in 2015, when 130 liver procedures were conducted. In the analysed period, 746 patients were treated by liver transplantation, 206 of whom were elderly patients, which makes every forth patient an elderly one. The indications for liver transplantation in the group of elderly patients were primary liver neoplasm, 91 of them (44.2%), followed by alcohol liver disease, 61 of them (29.6%), while other indications accounted for 26.2% (54 patients).

The mortality rate during the procedure and during the post-transplantation follow-up period was 31% in this age group (64 patients died). The main causes of death were infections, sepsis, and multiorgan failure.

DISCUSSION

Liver transplantation is a method which is used increasingly often and with more success in the treatment of patients with end-stage irrevers-

(14). Iako je broj transplantacija u stalnom porastu, i dalje je puno veći broj bolesnika kojima je potrebna transplantacija od broja učinjenih (15). Univerzalni problem u cijeloj transplantacijskoj medicini, a time i u transplantaciji jetre je nedostatak davatelja. To bi se moglo popraviti podizanjem svijesti populacije o potrebi darivanja organa te o izvrsnosti liječenja ovom metodom (16).

Starenjem populacije povećava se broj bolesnika starijih od 65 godina kojima se transplantacijom jetre može spasiti život (17). Pri tome je poznato da je kod ovih bolesnika komorbiditet značajniji te posttransplantacijski mortalitet veći nego kod mlađih bolesnika (18).

Za dalje poboljšanje posttransplantacijskog preživljenja, uz sve napretke koje donosi razvoj medicinske znanosti, sve veću ulogu imat će socijalna-psihološka potpora bliskog okruženja odnosno obitelji koja je od iznimnog značenja za psihički i tjelesni oporavak nakon kirurškog zahvata (19).

Brzim oporavkom te kraćim boravkom u bolnici nakon kirurškog zahvata smanjuje se rizik infekcija koje su i dalje vodeća komplikacija u postoperacijskom oporavku, te povećavaju mortalitet osobito u prvom postoperacijskom mjesecu kada bolesnici primaju visoke doze imunosupresivne terapije (20).

Osim rizika infekcije, a ovisno o indikaciji za transplantaciju jetre, odnosno o osnovnoj bolesti, postoje i drugi rizici. Takav je, primjerice, rizik od recidiva alkoholne bolesti jetre (zbog ponovne konzumacije alkohola), te je kod takvih bolesnika nužan daljnji psihijatrijski tretman.

ZAKLJUČAK

U zadnje se vrijeme više važnosti pridaje biološkoj kondiciji nego kronološkoj životnoj dobi.

Kao zaključak može se reći da životna dob bolesnika nije kontraindikacija za transplantacij-

ible liver failure (14). Although the number of liver transplantations is steadily rising, the number of patients that are candidates for this type of treatment still exceeds the number of transplantations (15). As is the case with other organs, there is a lack of organ-donors. This could be improved by preventive educational activities about the need for organ donation and the improvement of treatment of patients with end-stage liver failure using this method (16).

As the population ages, the number of elderly patients suitable for liver transplantation is also rising (17). It is well known that these patients often have significant comorbidity and higher post-transplantation mortality rates (18).

In the improvement of post-treatment survival, along with all the advantages provided by the development of medical science, the social-psychological support of the environment and the family will have an increasingly important role in postoperative recovery of such patients (19).

It is well-known that shorter periods of hospitalization carry a lower risk for infection, which is the most significant and serious complication in the postoperative recovery phase (20).

Beside the risk of infection, there are other post-transplantation risks. For example, one such risk is the recurrence of alcoholic liver disease (due to re-consumption of alcohol), and such patients require further psychiatric treatment.

CONCLUSION

In recent times, increasingly greater importance has been given to biological fitness rather than chronological age.

In conclusion, it can be said that the age of the patient is not a contraindication for liver trans-

sko liječenje završne faze jetrene bolesti. Na životnu dob ni u kom slučaju ne gledamo kao na izolirani negativni prognostički čimbenik, a osobito ne u bolesnika kod kojih je transplantacija jetre metoda koja spašava život.

Kao jedan od centara izvrsnosti u transplantacijskom liječenju uvijek smo skloniji bolesniku reći *Da* nego *Ne*, pogotovo kada je transplantacija jedini izbor i jedina metoda liječenja bolesnika.

plantation as a method of treating end-stage liver disease. Age itself is not a contraindication for liver transplantation and is not considered negative prognostic factor in any patient, especially not in elderly patients for whom liver transplantation would be lifesaving procedure.

As a centre of excellence, we always tend to say Yes rather than No, especially when liver transplantation is the only choice and the only method of treating patients.

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