

Pandemija COVID-19: vpliv na presaditev jeter v Sloveniji

COVID-19 pandemic: influence on liver transplantation in Slovenia

Blaž Trotovšek*

Klinični oddelek za abdominalno kirurgijo, Kirurška klinika, UKC Ljubljana

Gastroenterolog 2021; suplement 2: 31–34

Ključne besede: pandemija, Covid-19, presaditev jeter

Key words: pandemic, Covid-19, liver transplantation

IZVLEČEK

Uvod: Pandemijo Korona-virusne bolezni 2019 (Covid-19) povzroča korona-virus 2 hudega akutnega respiratornega sindroma (SARS-CoV-2). Težavnost obolenja in rezultat zdravljenja okužbe s Covid-19 je zelo odvisen od spremljajočih bolezni, kot so sladkorna bolezen, kardiovaskularna obolenja, arterijska hipertenzija, kronične bolezni ledvic, obolenja pljuč in starost. Ob nedvomnih dokazih o vplivu kroničnih obolenj na težavnost poteka okužbe s SARS-CoV-2, študije niso jasno dokazale vpliva osnovne bolezni jeter na izhod zdravljenja. Navkljub nadaljevanju pandemije Covid-19, so podatki o klinični sliki, poteku in prognozi bolezni pri pacientih po presaditvi organov pomanjkljivi in statistično neznačilni. Pacienti po presaditvi jeter (PJ) so ob okužbi Covid-19 izpostavljeni večjemu tveganju za zaplete in smrt zaradi kroničnega zdravljenja z zaviralci imunskega odgovora in spremljajočih bolezni.

Najpogostejši klinični znaki ob okužbi Covid-19 pri pacientih po PJ so povišana telesna temperatura, dihalna stiska in driska. Sprejem v bolnišnico je potreben skoraj pri 80 % pacientov s Covid-19 okužbo in

ABSTRACT

Introduction: Coronavirus disease-2019 (Covid-19) is a global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The severity and outcomes of Covid-19 infection are dependent on comorbidities such as diabetes mellitus, cardiovascular diseases including hypertension, kidney disease, pulmonary disease, and age. However, the presence of the underlying liver disease seems to have lesser impact on the outcome of Covid-19 infected patients. Notwithstanding the ongoing Covid-19 pandemic, information on its clinical presentation and prognosis in organ transplant recipients remains limited and often inconclusive. Liver transplant (LT) recipients may be at increased risk for adverse outcomes with Covid-19 infection because of chronic immunosuppression and associated comorbidities. The literature describing clinical presentation, treatments, and outcomes in LT recipients with Covid-19 is still scarce.

The most common clinical signs in LT recipients with Covid-19 infection are fever, dyspnea and diarrhea. Hospitalization is required in almost 80% of

*doc. dr. Blaž Trotovšek, dr. med

Klinični oddelek za abdominalno kirurgijo, Kirurška klinika, UKC Ljubljana, Zaloška cesta 7, 1000 Ljubljana

E-pošta: blaz.trotovsek@kelj.si

tri četrtine pacientov po PJ bo bolelo za zmerno ali hudo obliko bolezni, kar zahteva intenzivno podporno zdravljenje in tudi ukinitvev ali prilagoditev zdravljenja z zaviralci imunskega odziva.

Dihalna stiska ob sprejemu v bolnišnico, sladkorna bolezen in starost nad 60 let so bili značilno povezani s povečano umrljivostjo. Srednji čas od pojava simptomov pri pacientih po PJ do smrti je bil 12 dni. Umrljivost je bila še večja pri pacientih z visokim krvnim tlakom in pri tistih pacientih, ki so v času okužbe Covid-19 prejeli kortikosteroide. Smrtnost pacientov po PJ je v nekaterih raziskavah dosegla celo 20 %.

Pri cepljenju pacientov po PJ proti Covid-19 ostaja nekaj nejasnosti. Vse študije cepiv proti okužbi Covid-19 so kot izključitveni dejavnik navajale imunosupresijo. Aktivno in zgodnje cepljenje pacientov s kroničnimi boleznimi jeter ali po PJ naj bi zmanjšalo z boleznijo povezane zaplete in zagotovilo optimalni odgovor na cepljenje. Cepljenje med zdravljenjem akutne zavrtnitve ni priporočljivo. Cepiva so varna, a se priporoča izogibanje uporabe živih cepiv pri pacientih z zavrtim imunskim odzivom. Kandidatom za PJ se priporoča cepljenje vsaj 4 tedne pred PJ ob izogibanju uporabe živih cepiv v tem obdobju.

Metode: Opravljena je bila retrospektivna analiza števila okužb in precepljenosti pacientov na čakalni listi za presaditev jeter in prejemnikov, pri katerih je bila PJ opravljena od začetka leta 2018 dalje.

Rezultati: V marcu 2020, po razglasitvi pandemije in skoraj popolnemu angl. lockdownu, je sledilo prilagajanje tako programa za odvzem jeter in tkiv kot tudi programov presaditve organov. Kratko obdobje na začetku pandemije je program presaditve izvajal le najnujnejše, življenje rešujoče presaditve, tudi jeter, zaradi nejasnosti razvoja epidemije v Sloveniji. Navkljub temu smo doma presadili vse pridobljene jetrne presadke in v primerjavi s številnimi centri po Evropi, ki so morali prekiniti transplantacijsko dejavnost zaradi preobremenjenosti zdravstvenih sistemov, ohranili dobro delujoč program. Uspešen nadzor šte-

cases. Severity of disease varies among different groups of LT recipients but almost 75% has moderate or severe disease requiring intensive treatment and commonly (> 50%) modification of immunosuppression. Dyspnea on presentation, diabetes mellitus, and age 60 years or older were significantly associated with increased mortality with a trend to higher mortality rate observed in those with hypertension and those receiving corticosteroids at the time of Covid-19 diagnosis. The case fatality rate in some studies was up to 20%. Described median time from symptoms to death was approximately 12 days.

There are some concerns about Covid-19 vaccination in LT patients. All trials listed systemic immunosuppression as exclusion criteria. Active vaccination of patients with chronic liver disease and LT recipients should reduce vaccine-preventable illnesses and ensure optimal vaccine response. Vaccines should not be given during treatment for acute rejection. Vaccines are safe, however live vaccines should be avoided in immunosuppressed patients. LT candidates should be vaccinated at least 4 weeks prior to LT and should not receive live vaccines during this period.

Methods: Retrospective analysis of frequency and severity of Covid-19 infection in patients on waiting list for liver transplantation and recipients in whom LT was performed during last 3 years was performed in our center. Status of vaccination in this cohort was also evaluated.

Results: Immediately after the first lockdown in March 2020 in Slovenia, a short period of restriction in programs of multi-organ procurement and transplantation of solid organs followed. Very fast the restrictions were abandoned and normal activity was resumed with good results (9 LT in 3 months). In 2020 24 LT were performed, which signifies the drop of 10% annually, mainly due to the intensive drop in all activities (enlistment of recipients, potential donor recognition and number of multi-organ procurements) during second wave.

vila okužb v obdobju 1. vala Covid-19 in relativno nizka zasedenost bolnišnic, sta omogočila skoraj nemoteno delovanje programa. Velika večina presaditev (20/24) je bila izvedena pred začetkom drugega vala okužb. V mesecih prvega zaprtja države smo uspešno presadili 9 jeter, kar je predstavljalo rekordno število na milijon prebivalcev v področju Eurotransplanta. Zgodbe o uspehu med drugim valom okužb Covid-19 nismo ponovili, saj je prišlo do drastičnega upada števila presaditev jeter. Visoka precepljenost med čakajočimi na PJ in med prejemniki, ki so organ prejeli v zadnjih treh letih vliva nekaj optimizma. Med pacienti na čakalni listi je precepljenost 91,7 % in med prejemniki 85 %. Med pacienti uvrščenimi na čakalno listo za PJ med 1.3.2020 in 31.8.2021 smo zabeležili 4 okužbe s SARS-CoV-2 in nihče ni zbolel za težjo obliko Covid-19. Med prejemniki po PJ se je okužilo 8,5 % pacientov. Hospitalizacijo je potrebovalo 60 % pacientov s Covid-19 (3/5) in samo en pacient je potreboval intenzivno zdravljenje. Vsi okuženi so okužbo preživeli, na kar gotovo vpliva tudi nizko število opazovanih pacientov.

Zaključki: Cepljenje pacientov s kronično okvaro jeter in njihovih sorodnikov, socialna distanca, pravilna uporaba zaščitnih sredstev in higiena rok, so nujni postopki za preprečevanje okužb v tej skupini ogroženih pacientov. Pri starejših pacientih po PJ s sladkorno boleznijo in povišanim krvnim tlakom, na vzdrževalnem zdravljenju s kortikosteroidi in oteženim dihanjem, potrebujejo intenziven nadzor in zgodnjo prepoznavo slabšanja zdravstvenega stanja, zaradi zvišanega tveganja za zaplete in umrljivost. Priporočena je prireditev imunosupresivnega zdravljenja pri vseh pacientih po PJ z razvitimi simptomi okužbe z virusom SARS-CoV-2.

In the future high level of vaccination among the recipients on the waiting list (91,7%) preserves hope that the program of LT will continue during catastrophic 4th wave in Slovenia. Vaccination rate against SARS-CoV-2 among recipients who were transplanted since 2018 is 85% and is significantly higher than in general population. Among the patients enlisted on LT waiting list during 1.3.2020 and 31.8.2021, 4 of them had Covid-19 infection. None of them had severe form of Covid-19 disease. 8,5% (5/59) of patients who were transplanted in last 3 years were infected with SARS-CoV-2. 3 patients (60%) were hospitalized and one of them was treated in ICU. There was no mortality in our group of patients, probably due to the low number of patients.

Conclusions: Vaccination of patient and close relatives, social distance, masks and hygiene are the cornerstones of prevention in pandemic of Covid-19. Older LT patients with Covid-19 infection, with diabetes or hypertension, who are on maintenance corticosteroids and describing breathlessness should be aggressively monitored for signs of deterioration because of the risk for mortality.

Literatura

1. Fernández-Ruiz M, Andrés A, Loinaz C, Delgado JF, López-Medrano F, San Juan R, et al. COVID-19 in solid organ transplant recipients: A single center case series from Spain. *Am J Transplant.* 2020;20(7):1849–58.
2. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet.* 2020;396:27–38.
3. Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. *Am J Transplant.* 2020;20(7):1800–8.
4. Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. *Hepatology.* 2020;72(1):287–304.

5. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect.* 2020 ;81(2):16–25.
6. Kulkarni AV, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, et al. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther.* 2020;52(4):584–99.
7. Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E. COVID-19 and solid organ transplantation: a review article. *Transplantation.* 2021;105(1):37–55.
8. Kulkarni AV, Parthasarathy K, Kumar P, Sharma M, Reddy R, Venkata KCA, et al. Early liver transplantation after COVID-19 infection: the first report. *Am J Transplant.* 2021;21(6):2279–84.
9. Kulkarni AV, Tevethia HV, Premkumar M, Arab JP, Candia R, Kumar K, et al. Impact of COVID-19 infection on liver transplant recipients – A systematic review and meta-analysis. *EclinicalMedicine.* 2021;38:1–11.
10. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol.* 2020;5(6):532–3.
11. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. *J Hepatol.* 2021;74(3):567–77.
12. Shalimar, Elhence A, Vaishnav M, Kumar R, Pathak P, Soni KD, et al. Poor outcomes in patients with cirrhosis and Corona Virus Disease-19. *Indian J Gastroenterol.* 2020;39(3):285–91.
13. Nacif LS, Zanini LY, Waisberg DR, Pinheiro RS, Galvao F, Andraus W, et al. COVID-19 in solid organ transplantation patients: a systematic review. *Clinics.* 2020;75:1–11.
14. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, et al. Epidemiology of COVID-19: a systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol.* 2021;93(3):1449–58.
15. Belli LS, Fondevila C, Cortesi PA, Conti S, Karam V, Adam R, et al. Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR multi-center European study. *Gastroenterology.* 2020;160(4):1151–63.
16. Marjot T, Webb GJ, Barritt AS, Gines P, Lohse AW, Moon AM, et al. SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question. *Lancet Gastroenterol Hepatol.* 2021;6(3):156–8.
17. Boettler T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep.* 2020;2(3):100–13.