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慢性肝病患者接种新型冠状病毒疫苗相关研究进展

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摘　要

新型冠状病毒肺炎(Coronavirus Disease 2019, COVID-19)由于其高传播率及人群普遍易感性成为威胁生命的全球健康负担。全国广泛推行新型冠状病毒疫苗接种以产生群体免疫。我国现存超3亿的慢性肝病患者，有研究表明，慢性肝病患者较健康人群对COVID-19有更高的易感性，且慢性肝病患者感染COVID-19后的重症率和死亡率升高，接种新冠疫苗可以有效降低新冠感染后的重症率和死亡率。目前有部分关于这一特殊人群接种新冠疫苗的安全性和有效性研究。本综述叙述了慢性肝病与COVID-19之间的关系，也叙述了新冠肺炎疫苗在慢性肝病这一特殊人群中的安全性和有效性。

关键词

新型冠状病毒肺炎，新型冠状病毒疫苗，慢性肝病，肝损伤

Research Progress of COVID-19 Vaccination in Patients with Chronic Liver Diseases

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Abstract

Coronavirus Disease 2019 (COVID-19) has become a life-threatening global health burden due to

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its rapid transmission rate and general susceptibility. Vaccination against SARS-Cov-2 was actively promoted worldwide. There are more than 300 million patients with chronic liver diseases in China. Patients with chronic liver diseases have a higher susceptibility to COVID-19 than healthy people. They are considered to be at a high risk for severe COVID-19 and death. SARS-Cov-2 vaccination can reduce the disease severity and mortality effectively. There are some studies on the safety and efficacy of COVID-19 vaccination in patients with chronic liver diseases. This review focuses on the role of COVID-19 in chronic liver diseases and the safety and efficacy of COVID-19 vaccination in this special population.

Keywords

COVID-19, SARS-CoV-2 Vaccine, Chronic Liver Diseases, Liver Injury

1. 引言

严重急性呼吸综合征冠状病毒 2 (Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2)是 2019 年首次发现的一种 RNA 病毒，它的传播导致了 COVID-19 大流行，造成了全球混乱。COVID-19 是威胁生命的全球健康负担，截至 2022 年 10 月，全球报告的新冠确诊病例超过 6.24 亿例，死亡超过 650 万例[1]。有慢性疾病和多种合并症的人群感染 COVID-19 后的死亡率显著[2] [3]。研究表明，慢性肝病患者感染新冠后容易发生肝损伤，且慢性肝病是新冠感染后住院时间延长和疾病加重的危险因素[4]。慢性肝病患者由于免疫功能紊乱和慢性生理应激，感染新冠后死亡风险显著增加(OR = 2.8; 95%CI 1.9~4.0; P < 0.001) [5] [6] [7]。一项系统综述和荟萃分析显示，合并慢性肝病的 COVID-19 患者发生重症新冠肺炎的风险(合并 OR = 2.44; 95%CI, 1.89~3.16)和死亡(合并 OR = 2.35; 95%CI 1.85~3.00)的概率显著升高[8]。大量研究证实，新冠疫苗可以有效降低新冠肺炎的感染率、新冠感染后的重症率和死亡率[3] [9] [10]。

2. 慢性肝病和新冠肺炎

既往存在的慢性肝病会影响 SARS-CoV-2 感染的结局和严重程度[11] [12] [13]。慢性肝病与死亡风险增加相关，尤其是肝硬化会使 COVID-19 死亡风险增加约 5 倍[7]。COVID-19 相关死亡率在 Child-Pugh A 级患者中为 22%，上升到 Child-Pugh B 级患者的 39%，在 Child-Pugh C 级患者中为 54% [14]。感染 COVID-19 的肝硬化患者可能会加重肝功能障碍，这些患者发生急性肝功能衰竭风险较高(46%)。此外，乙型肝炎和丙型肝炎患者可能会因 COVID-19 本身或激素等治疗而发生再激活[15]。一项荟萃分析报告乙型病毒性肝炎患者因 COVID-19 住院死亡的概率增加 2 倍(OR = 2.04, 95%CI 1.49~2.79)，且更有可能发展为重症(OR = 1.90, 95%CI 1.32~2.73) [16]。自身免疫性肝炎(Autoimmune hepatitis, AIH)或其他自身免疫性肝病是否促进重症新冠肺炎尚不确定，但有研究显示 AIH 患者没有增加 COVID-19 相关死亡率[17]。既往有肝病基础的患者新冠肺炎感染率和新冠肺炎相关死亡的风险更高，主要原因有肝硬化相关免疫功能障碍(Cirrhosis-associated immune dysfunction, CAID)，免疫失调导致持续的全身炎症反应以及对细菌和病毒感染的易感性增加[18] [19]。与新冠肺炎发病机制有关的细胞因子风暴有可能加重肝脏损伤，从而导致凝血异常和微血栓形成[20]。

3. 新型冠状病毒疫苗的安全性

目前全球使用的主要的新冠肺炎疫苗包括辉瑞、莫德纳和牛津－阿斯利康生产的疫苗。主要包括mRNA 疫苗(BNT162b2 mRNA, mRNA-1273 mRNA)、病毒载体疫苗(AZD1222)、灭活病毒疫苗(CoronaVac)、减毒疫苗、蛋白质亚单位疫苗和重组 DNA 疫苗[21]。新冠肺炎疫苗的常见副作用包括注射部位疼痛、一过性发热、头痛和疲劳[22]。一项关于 SARS-CoV-2 灭活疫苗的临床试验中描述了该灭活疫苗的安全性，在 144 名疫苗接受者中，有 42 人(29%)在接种后的前 7 天内报告了至少一次不良反应。所有不良反应均为轻度或中度，且都为自限性的[23]。随着新冠疫苗的广泛接种以来，有报道许多罕见的不良事件，包括超敏反应、血栓性血小板减少性紫癜和免疫性血栓性血小板减少症[24]。也有一些新冠肺炎疫苗接种后器官特异性或系统免疫相关的副作用的报道。这些副作用包括免疫介导性肝损伤，类似于 AIH [25]。

香港报道了一项关于接种新冠疫苗后发生急性肝损伤的大规模人群研究，在 2,343,288 例接种疫苗的人群中，接种 BNT162b2 疫苗的有 307 例和 521 例(每 10 万人年 335 例和 334 例)在第一次和第二次疫苗接种后 56 天内发生急性肝损伤，接种 CoronaVac 疫苗的有 304 例和 474 例(每 10 万人年 358 例和 403 例)在第一次和第二次疫苗接种后 56 天内发生急性肝损伤，SARS-CoV-2 感染后 56 天内的 ALI 病例数为每 10 万人年 32,997 例，这说明接种新冠肺炎疫苗后的急性肝损伤发生率明显低于 SARS-CoV-2 感染后。与非暴露期相比，BNT162b2 第一剂(IRR 0.800; 95%CI 0.680~0.942)和第二剂(IRR 0.944; 95%CI 0.816~1.091)或 CoronaVac 第一剂(IRR 0.689; 95%CI 0.588~0.807)和第二剂(IRR 0.905; 95%CI 0.781~1.048)的 56 天风险期没有观察到风险增加。这说明接种新冠疫苗后发生急性肝损伤的风险并没有增加[26]。其他有关于疫苗后诱导免疫介导性肝损伤的报道，提出 SARS-CoV-2 刺突蛋白抗体与人体组织的交叉反应可能触发自身免疫[27]。一项回顾新冠疫苗接种后诱导免疫介导性肝损伤的文献综述中，发现 1/4 的患者接种新冠疫苗前就存在自身免疫性疾病(自身免疫性肝炎、桥本甲状腺炎、原发硬化性胆管炎)。疫苗后发生免疫介导性肝损伤病例的主要是老年女性，大多数病例类似于自身免疫性肝炎，而且对类固醇的反应良好。新冠疫苗后发生免疫介导性肝损伤罕见，很难确定疫苗接种和肝脏损伤之间的因果关系。事实上，怀孕后的状态、他汀类药物的使用以及报告病例中包括的伴随的自身免疫性疾病史可能是主要的混杂因素[28]。一例病例报道疫苗诱导的自身免疫性肝炎患者在肝脏活检中出现晚期纤维化，这表明在接种疫苗之前存在慢性肝病[29]。报告疫苗后免疫介导性肝损伤的病例大都缺乏疫苗接种前的实验室数据，因此，不能排除先前存在的肝炎。

4. 慢性肝病患者接种新冠疫苗的有效性和安全性

一项关于新冠疫苗在慢性肝病患者和肝移植受者中的免疫原性的荟萃分析显示，慢性肝病患者接种两剂新冠疫苗后的体液免疫应答检出率为 95% (95%CI = 88%~99%)，接种 2 剂次疫苗后，慢性肝病患者和健康对照的体液免疫应答率相似(RR = 0.96; 95%CI = 0.90~1.02; P = 0.14) [30]。

4.1. 肝硬化与新冠疫苗

美国的 Thuluvath 等人的研究表明，75%的无肝硬化的慢性肝病患者和 77%的肝硬化患者接种新冠疫苗后可以足够的抗体[31]。但是，肝硬化患者的抗体滴度会下降得更快[32]。这可能与接种疫苗后 T 细胞反应较弱有关[33]。肝硬变患者 CD27+记忆 B 细胞计数的减少也可能解释了疫苗在这类患者中疗效降低的原因[34]。一项关于 Sinovac-CoronaVac 疫苗的报道中，慢性肝病患者的免疫原性(77.3%)低于健康对照组(90.3%)，是否存在肝硬化对抗体阳性率没有影响[35]。在该报告中，慢性肝病患者接种新冠疫苗的安全性与健康对照组相似。一份关于 BNT162b2mRNA、mRNA1273 和 Ad26.COV2.S 疫苗的报告显示，接种新冠疫苗的肝硬化患者中与新冠肺炎相关的死亡率显著降低(HR: 0.21; 95%CI: 0.11~0.42) [36]。这表明，

肝硬化患者接种新冠疫苗有效，但应该注意，抗体随着时间的推移会下降，保护性减弱，需要注意加强注射的时间问题。安全性方面，曹等人报告说，在接受至少一剂 SARS-CoV-2 疫苗接种的 85 名失代偿期肝硬化患者中，只有一名患者(1.2%)出现了需要住院的不良反应[37]。Baksis 等人报告了 87 名肝病患者(包括肝硬化患者)和 40 名对照组注射的 mRNA 疫苗的安全性没有显著差异[38]。

4.2. 肝移植受者与新冠疫苗

有研究表明，肝移植受者接种 mRNA 疫苗 2 周后的体液和细胞免疫较健康人显著减弱[39] [40]，免疫原性显著降低[41]，抗体血清转换率低[42]，联合免疫抑制疗法是疫苗接种反应性降低的预测因子[43]，肝移植患者在接种 mRNA 疫苗后抗体滴度也迅速下降[42]。一项多中心队列研究表明，mRNA 疫苗可以降低肝移植受者和肝硬化患者的 SARS-CoV-2 感染率、有症状新冠肺炎的发生率和死亡率[36]。关于新冠疫苗在慢性肝病患者和肝移植受者中的免疫原性的荟萃分析显示，肝移植受者接种两剂新冠疫苗后的体液免疫应答检出率为 66% (95%CI = 57%~74%)，其体液免疫应答率低于健康对照者(RR = 0.68; 95%CI = 0.59~0.77; P < 0.01) [30]。肝移植受者接种疫苗后免疫性较低及抗体滴度下降快，但其安全性良好，且能降低新冠感染发病率，感染后的重症率及死亡率，指南仍推荐肝移植受者接种新冠疫苗及加强注射[33] [44] [45]。

4.3. 肝癌与新冠疫苗

肝癌患者是重症新冠肺炎的高危人群[12]。接受过包括肝癌在内的实体瘤治疗的大多数患者在接种两剂疫苗后均表现出充分的体液应答。然而，化疗期间接种疫苗往往产生较低的抗体水平，导致一小部分患者对新冠疫苗的应答欠佳[46] [47]。同样的，抗体滴度随时间下降，免疫力降低[48]。

4.4. 慢乙肝和非酒精性脂肪肝与新冠疫苗

关于病毒性肝炎，我国两项研究表明慢性乙型病毒型肝炎患者接种新冠疫苗的安全性好，其免疫反应不受核苷类似物治疗的影响，抗体血清转换率与健康人群相似，指南建议慢乙肝治疗期间也应进行疫苗接种[49] [50]。一项关于非酒精性脂肪肝患者接种灭活疫苗安全性和免疫原性的多中心研究中，接种后 7 天和 28 天内的不良反应发生率分别为 24.9%和 29.4%，95.5%的患者中检测到中和抗体，并显示中和抗体滴度持续较久[51]。鉴于非酒精性脂肪肝是重症 COVID-19 的危险因素，这一患者人群也有必要积极接种新冠疫苗[52] [53] [54]。

4.5. 自身免疫性肝病与新冠疫苗

关于自身免疫性肝炎患者接种新冠疫苗的研究中，Duengelhoef 等人报道，94 例自身免疫性肝炎患者接种第二剂疫苗后，有 91 例(97%)血清抗体阳性，但与健康人或原发性胆汁性胆管炎、原发性硬化性胆管炎相比，自身免疫性肝炎患者接种新冠疫苗后表现出对新冠刺突蛋白的特异性 T 细胞受损和较低的抗体水平[55]。一项随访自身免疫性肝炎患者接种 mRNA 疫苗后抗体反应的研究表明，在第二次和第三次接种后，两组都产生了相当的抗体[56]。我国一项研究表明 SARSCoV-2 灭活疫苗在自身免疫性肝病患者中具有良好的安全性，但免疫原性受到影响，使用免疫抑制剂估计会使 SARS-CoV-2 疫苗抗体反应差的风险增加 3-5 倍[57]。因此，推荐自身免疫性肝炎患者考虑早期接种加强疫苗。

5. 总结

慢性肝病人群与接种新冠疫苗有关的不良事件大多性质轻微且为自限性的，与普通人群中报告的不良事件发生率相似，这一人群接种新冠疫苗后发生肝损伤也相对少见。慢性肝病人群对新冠疫苗的免疫

反应较普通人群低，疫苗保护的有效率和持久性低。慢性肝病患者对新冠疫苗的安全性好，其感染新冠肺炎后病情严重程度和死亡率增加，接种新冠疫苗可以有效降低重症率和死亡率。因此，积极接种疫苗及加强注射对这类人群具有重要意义。

参考文献

[1] Whittaker, C., Walker, P., Alhaffar, M., *et al*. (2021) Under-Reporting of Deaths Limits Our Understanding of True Burden of COVID-19. *BMJ*, **375**, Article No. n2239. https://doi.org/10.1136/bmj.n2239

[2] Biswas, M., Rahaman, S., Biswas, T.K., *et al*. (2020) Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirology*, 1-12.

[3] Mukherjee, A., Kumar, G., Turuk, A., *et al*. (2023) Vaccination Saves Lives: A Real-Time Study of Patients with Chronic Diseases and Severe COVID-19 Infection. *QJM*: *An International Journal of Medicine*, **116**, 47-56. https://doi.org/10.1093/qjmed/hcac202

[4] Cichoż-Lach, H. and Michalak, A. (2021) Liver Injury in the Era of COVID-19. *World Journal of Gastroenterology*, **27**, 377-390. https://doi.org/10.3748/wjg.v27.i5.377

[5] Alqahtani, S.A., Aljumah, A.A., Hashim, A., *et al*. (2020) Principles of Care for Patients with Liver Disease during the Coronavirus Disease 2019 (COVID-19) Pandemic: Position Statement of the Saudi Association for the Study of Liver Disease and Transplantation. *Annals of Saudi Medicine*, **40**, 273-280. https://doi.org/10.5144/0256-4947.2020.273

[6] Boettler, T., Marjot, T., Newsome, P.N., *et al*. (2020) Impact of COVID-19 on the Care of Patients with Liver Disease: EASL-ESCMID Position Paper after 6 Months of the Pandemic. *JHEP Reports*, **2**, Article ID: 100169. https://doi.org/10.1016/j.jhepr.2020.100169

[7] Singh, S. and Khan, A. (2020) Clinical Characteristics and Outcomes of Coronavirus Disease 2019 among Patients with Preexisting Liver Disease in the United States: A Multicenter Research Network Study. *Gastroenterology*, **159**, 768-771. https://doi.org/10.1053/j.gastro.2020.04.064

[8] Nagarajan, R., Krishnamoorthy, Y., Rajaa, S. and Hariharan, V.S. (2022) COVID-19 Severity and Mortality among Chronic Liver Disease Patients: A Systematic Review and Meta-Analysis. *Preventing Chronic Disease*, **19**, E53. https://doi.org/10.5888/pcd19.210228

[9] Steele, M.K., Couture, A., Reed, C., *et al*. (2022) Estimated Number of COVID-19 Infections, Hospitalizations, and Deaths Prevented among Vaccinated Persons in the US, December 2020 to September 2021. *JAMA Network Open*, **5**, e2220385. https://doi.org/10.1001/jamanetworkopen.2022.20385

[10] Tulimilli, S.V., Dallavalasa, S., Basavaraju, C.G., *et al*. (2022) Variants of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Vaccine Effectiveness. *Vaccines*, **10**, Article No. 1751. https://doi.org/10.3390/vaccines10101751

[11] Ioannou, G.N., Liang, P.S., Locke, E., *et al*. (2021) Cirrhosis and Severe Acute Respiratory Syndrome Coronavirus 2 Infection in US Veterans: Risk of Infection, Hospitalization, Ventilation, and Mortality. *Hepatology*, **74**, 322-335. https://doi.org/10.1002/hep.31649

[12] Kim, D., Adeniji, N., Latt, N., *et al*. (2021) Predictors of Outcomes of COVID-19 in Patients with Chronic Liver Disease: US Multi-Center Study. *Clinical Gastroenterology and Hepatology*, **19**, 1469-1479. https://doi.org/10.1016/j.cgh.2020.09.027

[13] Moon, A.M., Webb, G.J., Aloman, C., *et al*. (2020) High Mortality Rates for SARS-CoV-2 Infection in Patients with Pre-Existing Chronic Liver Disease and Cirrhosis: Preliminary Results from an International Registry. *Journal of Hepatology*, **73**, 705-708. https://doi.org/10.1016/j.jhep.2020.05.013

[14] Marjot, T., Moon, A.M., Cook, J.A., *et al*. (2021) Outcomes Following SARS-CoV-2 Infection in Patients with Chronic Liver Disease: An International Registry Study. *Journal of Hepatology*, **74**, 567-577. https://doi.org/10.1016/j.jhep.2020.09.024

[15] Sagnelli, C., Montella, L., Grimaldi, P., *et al*. (2022) COVID-19 as Another Trigger for HBV Reactivation: Clinical Case and Review of Literature. *Pathogens*, **11**, Article No. 816. https://doi.org/10.3390/pathogens11070816

[16] Yu, Y., Li, X. and Wan, T. (2023) Effects of Hepatitis B Virus Infection on Patients with COVID-19: A Meta-Analysis. *Digestive Diseases and Sciences*, **68**, 1615-1631. https://doi.org/10.1007/s10620-022-07687-2

[17] Marjot, T., Buescher, G., Sebode, M., *et al*. (2021) SARS-CoV-2 Infection in Patients with Autoimmune Hepatitis. *Journal of Hepatology*, **74**, 1335-1343. https://doi.org/10.1016/j.jhep.2021.01.021

[18] Chavez-Tapia, N.C., Torre-Delgadillo, A., Tellez-Avila, F.I. and Uribe, M. (2007) The Molecular Basis of Susceptibility to Infection in Liver Cirrhosis. *Current Medicinal Chemistry*, **14**, 2954-2958. https://doi.org/10.2174/092986707782794041

[19] Sharma P., Kumar A., Anikhindi S., *et al*. (2021) Effect of COVID-19 on Pre-Existing Liver Disease: What Hepatologist Should Know? *Journal of Clinical and Experimental Hepatology*, **11**, 484-493. https://doi.org/10.1016/j.jceh.2020.12.006

[20] Premkumar, M. and Kedarisetty, C.K. (2021) Cytokine Storm of COVID-19 and Its Impact on Patients with and without Chronic Liver Disease. *Journal of Clinical and Translational Hepatology*, **9**, 256-264. https://doi.org/10.14218/JCTH.2021.00055

[21] Khandker, S.S., Godman, B., Jawad, M.I., *et al*. (2021) A Systematic Review on COVID-19 Vaccine Strategies, Their Effectiveness, and Issues. *Vaccines*, **9**, Article No. 1387. https://doi.org/10.3390/vaccines9121387

[22] Amodio, E., Minutolo, G., Casuccio, A., *et al*. (2022) Adverse Reactions to Anti-SARS-CoV-2 Vaccine: A Prospective Cohort Study Based on an Active Surveillance System. *Vaccines*, **10**, Article No. 345. https://doi.org/10.3390/vaccines10030345

[23] Xia, S., Zhang, Y., Wang, Y., *et al*. (2021) Safety and Immunogenicity of an Inactivated SARS-CoV-2 Vaccine, BBIBP-CorV: A Randomised, Double-Blind, Placebo-Controlled, Phase 1/2 Trial. *The Lancet Infectious Diseases*, **21**, 39-51. https://doi.org/10.1016/S1473-3099(20)30831-8

[24] Novak, N., Tordesillas, L. and Cabanillas, B. (2022) Adverse Rare Events to Vaccines for COVID-19: From Hypersensitivity Reactions to Thrombosis and Thrombocytopenia. *International Reviews of Immunology*, **41**, 438-447. https://doi.org/10.1080/08830185.2021.1939696

[25] Chen, Y., Xu, Z., Wang, P., *et al*. (2022) New-Onset Autoimmune Phenomena Post-COVID-19 Vaccination. *Immunology*, **165**, 386-401. https://doi.org/10.1111/imm.13443

[26] Wong, C.K.H., Mak, L.Y., Au, I., *et al*. (2022) Risk of Acute Liver Injury Following the mRNA (BNT162b2) and Inactivated (CoronaVac) COVID-19 Vaccines. *Journal of Hepatology*, **77**, 1339-1348. https://doi.org/10.1016/j.jhep.2022.06.032

[27] Vojdani, A. and Kharrazian, D. (2020) Potential Antigenic Cross-Reactivity between SARS-CoV-2 and Human Tissue with a Possible Link to an Increase in Autoimmune Diseases. *Clinical Immunology*, **217**, Article ID: 108480. https://doi.org/10.1016/j.clim.2020.108480

[28] Roy, A., Verma, N., Singh, S., *et al*. (2022) Immune-Mediated Liver Injury Following COVID-19 Vaccination: A Systematic Review. *Hepatology Communications*, **6**, 2513-2522. https://doi.org/10.1002/hep4.1979

[29] Cao, Z., Gui, H., Sheng, Z., Xin, H. and Xie, Q. (2022) Letter to the Editor: Exacerbation of Autoimmune Hepatitis after COVID-19 Vaccination. *Hepatology*, **75**, 757-759. https://doi.org/10.1002/hep.32269

[30] Luo, D., Chen, X., Du, J., *et al*. (2023) Immunogenicity of COVID-19 Vaccines in Chronic Liver Disease Patients and Liver Transplant Recipients: A Systematic Review and Meta-Analysis. *Liver International*, **43**, 34-48. https://doi.org/10.1111/liv.15403

[31] Thuluvath, P.J., Robarts, P. and Chauhan, M. (2021) Analysis of Antibody Responses after COVID-19 Vaccination in Liver Transplant Recipients and Those with Chronic Liver Diseases. *Journal of Hepatology*, **75**, 1434-1439. https://doi.org/10.1016/j.jhep.2021.08.008

[32] Willuweit, K., Frey, A., Passenberg, M., *et al*. (2022) Patients with Liver Cirrhosis Show High Immunogenicity upon COVID-19 Vaccination but Develop Premature Deterioration of Antibody Titers. *Vaccines*, **10**, Article No. 377. https://doi.org/10.3390/vaccines10030377

[33] Ruether, D.F., Schaub, G.M., Duengelhoef, P.M., *et al*. (2022) SARS-CoV2-Specific Humoral and T-Cell Immune Response after Second Vaccination in Liver Cirrhosis and Transplant Patients. *Clinical Gastroenterology and Hepatology*, **20**, 162-172. https://doi.org/10.1016/j.cgh.2021.09.003

[34] Doi, H., Iyer, T.K., Carpenter, E., *et al*. (2012) Dysfunctional B-Cell Activation in Cirrhosis Resulting from Hepatitis C Infection Associated with Disappearance of CD27-Positive B-Cell Population. *Hepatology*, **55**, 709-719. https://doi.org/10.1002/hep.24689

[35] John, B.V., Sidney, B.A.T., Moon, A., *et al*. (2022) Effectiveness of COVID-19 Viral Vector Ad.26.COV2.S Vaccine and Comparison with mRNA Vaccines in Cirrhosis. *Clinical Gastroenterology and Hepatology*, **20**, 2405-2408. https://doi.org/10.1016/j.cgh.2022.05.038

[36] John, B.V., Deng, Y., Schwartz, K.B., *et al*. (2022) Postvaccination COVID-19 Infection Is Associated with Reduced Mortality in Patients with Cirrhosis. *Hepatology*, **76**, 126-138. https://doi.org/10.1002/hep.32337

[37] Cao, Z., Zhang, C., Zhao, S., *et al*. (2022) COVID-19 Vaccines in Patients with Decompensated Cirrhosis: A Retrospective Cohort on Safety Data and Risk Factors Associated with Unvaccinated Status. *Infectious Diseases of Poverty*, **11**, Article No. 56. https://doi.org/10.1186/s40249-022-00982-0

[38] Bakasis, A.-D., Bitzogli, K., Mouziouras, D., *et al*. (2022) Antibody Responses after SARS-CoV-2 Vaccination in Patients with Liver Diseases. *Viruses*, **14**, Article No. 207. https://doi.org/10.3390/v14020207

[39] Davidov, Y., Tsaraf, K., Cohen-Ezra, O., *et al*. (2022) Immunogenicity and Adverse Effects of the 2-Dose BNT162b2

Messenger RNA Vaccine among Liver Transplantation Recipients. *Liver Transplantation*, **28**, 215-223. https://doi.org/10.1002/lt.26366

[40] D'Offizi. G., Agrati. C., Visco-Comandini. U., *et al*. (2022) Coordinated Cellular and Humoral Immune Responses after Two-Dose SARS-CoV2 mRNA Vaccination in Liver Transplant Recipients. *Liver International*, **42**, 180-186. https://doi.org/10.1111/liv.15089

[41] Rabinowich, L., Grupper, A., Baruch, R., *et al*. (2021) Low Immunogenicity to SARS-CoV-2 Vaccination among Liver Transplant Recipients. *Journal of Hepatology*, **75**, 435-438. https://doi.org/10.1016/j.jhep.2021.04.020

[42] Sakai, A., Morishita, T. and Matsunami, H. (2022) Antibody Response after a Second Dose of the BNT162b2 mRNA COVID-19 Vaccine in Liver Transplant Recipients. *Transplant International*, **35**, Article ID: 10321. https://doi.org/10.3389/ti.2022.10321

[43] Timmermann, L., Globke, B., Lurje, G., *et al*. (2021) Humoral Immune Response following SARS-CoV-2 Vaccination in Liver Transplant Recipients. *Vaccines*, **9**, Article No. 1422. https://doi.org/10.3390/vaccines9121422

[44] Fix, O.K., Blumberg, E.A., Chang, K.M., *et al*. (2021) American Association for the Study of Liver Diseases Expert Panel Consensus Statement: Vaccines to Prevent Coronavirus Disease 2019 Infection in Patients with Liver Disease. *Hepatology*, **74**, 1049-1064. https://doi.org/10.1002/hep.31751

[45] Kamar, N., Abravanel, F., Marion, O., *et al*. (2021) Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *New England Journal of Medicine*, **385**, 661-662. https://doi.org/10.1056/NEJMc2108861

[46] Oosting, S.F., van der Veldt, A., Fehrmann, R., *et al*. (2022) Immunogenicity after Second and Third mRNA-1273 Vaccination Doses in Patients Receiving Chemotherapy, Immunotherapy, or Both for Solid Tumours. *The Lancet Oncology*, **23**, 833-835. https://doi.org/10.1016/S1470-2045(22)00203-0

[47] Peeters, M., Verbruggen, L., Teuwen, L., *et al*. (2021) Reduced Humoral Immune Response after BNT162b2 Coronavirus Disease 2019 Messenger RNA Vaccination in Cancer Patients under Antineoplastic Treatment. *ESMO Open*, **6**, Article ID: 100274. https://doi.org/10.1016/j.esmoop.2021.100274

[48] Levin, E.G., Lustig, Y., Cohen, C., *et al*. (2021) Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. *New England Journal of Medicine*, **385**, e84. https://doi.org/10.1056/NEJMoa2114583

[49] He, T., Zhou, Y., Xu, P., *et al*. (2022) Safety and Antibody Response to Inactivated COVID-19 Vaccine in Patients with Chronic Hepatitis B Virus Infection. *Liver International*, **42**, 1287-1296. https://doi.org/10.1111/liv.15173

[50] Xiang, T., Liang, B., Wang, H., *et al*. (2021) Safety and Immunogenicity of a SARS-CoV-2 Inactivated Vaccine in Patients with Chronic Hepatitis B Virus Infection. *Cellular & Molecular Immunology*, **18**, 2679-2681. https://doi.org/10.1038/s41423-021-00795-5

[51] Wang, J., Hou, Z., Liu, J., *et al*. (2021) Safety and Immunogenicity of COVID-19 Vaccination in Patients with Non-Alcoholic Fatty Liver Disease (CHESS2101): A Multicenter Study. *Journal of Hepatology*, **75**, 439-441. https://doi.org/10.1016/j.jhep.2021.04.026

[52] Hegyi, P.J., Vancsa, S., Ocskay, K., *et al*. (2021) Metabolic Associated Fatty Liver Disease Is Associated with an Increased Risk of Severe COVID-19: A Systematic Review with Meta-Analysis. *Frontiers in Medicine*, **8**, Article 626425. https://doi.org/10.3389/fmed.2021.626425

[53] Pan, L., Huang, P., Xie, X., *et al*. (2021) Metabolic Associated Fatty Liver Disease Increases the Severity of COVID-19: A Meta-Analysis. *Digestive and Liver Disease*, **53**, 153-157. https://doi.org/10.1016/j.dld.2020.09.007

[54] Singh, A., Hussain, S. and Antony, B. (2021) Non-Alcoholic Fatty Liver Disease and Clinical Outcomes in Patients with COVID-19: A Comprehensive Systematic Review and Meta-Analysis. *Diabetes & Metabolic Syndrome*: *Clinical Research & Reviews*, **15**, 813-822. https://doi.org/10.1016/j.dsx.2021.03.019

[55] Duengelhoef, P., Hartl, J., Ruther, D., *et al*. (2022) SARS-CoV-2 Vaccination Response in Patients with Autoimmune Hepatitis and Autoimmune Cholestatic Liver Disease. *United European Gastroenterology Journal*, **10**, 319-329. https://doi.org/10.1002/ueg2.12218

[56] Schneider, L., Schubert, L., Winkler, F., *et al*. (2022) SARS-CoV-2 Vaccine Response in Patients with Autoimmune Hepatitis. *Clinical Gastroenterology and Hepatology*, **20**, 2145-2147. https://doi.org/10.1016/j.cgh.2022.04.006

[57] Li, H., Wang, Y., Ao, L., *et al*. (2022) Association between Immunosuppressants and Poor Antibody Responses to SARS-CoV-2 Vaccines in Patients with Autoimmune Liver Diseases. *Frontiers in Immunology*, **13**, Article 988004. https://doi.org/10.3389/fimmu.2022.988004